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Risk factors for reading disability in families with rolandic epilepsy

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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 probands with RE (age range: 3.6–22 years) and their 159 siblings (age range: 1–29 years; 83 with EEG data) were singly ascertained in the US or UK through a proband affected by RE. We used a nested case–control design, multiple logistic regression, and generalized estimating equations to test the hypothesis of an 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: Reading disability 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 probands with RE, 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 characterization of RD in families with RE and on the effectiveness of standard oral-language and reading interventions.

1. Introduction

The existence of cognitive, behavioral, psychiatric, and somatic comorbidities is well documented in epilepsies of childhood. Some of

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these comorbidities are shared among children with epilepsies traditionally considered to have favorable prognoses, 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 (OR) — 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].

Reading disability is one of the most common neurodevelopmental conditions in childhood, with a prevalence in the general population ranging from 5 to 12% [5]. Reading disability 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]. Reading disability 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 overrepresented 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 probands with RE [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 probands with RE and siblings; and (ii) determine the evidence of 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 probands with RE. In a subset of siblings, we examined the evidence of an association of EEG focal sharp waves with RD.

2. Methods

2.1. Design

We conducted an observational study of probands with RE and their siblings with clinical data acquired at a single timepoint to determine the 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 probands unaffected by RD and siblings as controls.

2.2. Ascertainment

Typical probands with RE 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 and 2009 and from southeastern UK pediatric centers between 2009 and 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

Cases with RE were enrolled if they met stringent eligibility criteria including the following: 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 pediatrics-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, and 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).

Reading disability 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,

Table 1
Summary characteristics of probands with rolandic epilepsy 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