Rolandic Epilepsy

A Neuroradiological, Neuropsychological and Oromotor Study

BY

STAFFAN LUNDBERG
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Abstract

Rolandic epilepsy (RE) is the most common focal epilepsy syndrome in the pediatric age group with an onset between 3 and 13 years. The syndrome is defined by electro-clinically typical features and has been considered benign according to seizure remission before the age of 16 years.

The aim of this thesis was to investigate children with typical RE with different methods and to discuss the delineation of the syndrome. Thirty-eight children, aged 6–14 years, participated in one up to four studies.

Eighteen children were investigated with MRI. Hippocampal abnormalities were found in six (33%), volume asymmetry in five (28%) and high signal intensities on T2-weighted images in three (17%). Additionally, high signal intensities in T2-weighted images were revealed subcortically in temporal and frontal lobes bilaterally in five children (28%).

The hippocampal region was evaluated metabolically using proton magnetic resonance spectroscopy (1H-MRS) in 13 children with RE and 15 matched controls. A metabolic asymmetry of the hippocampal regions was found in the patients compared to controls indicating an abnormal neuronal function.

Seventeen children with RE and 17 matched controls were investigated with a neuropsychological test battery. The RE children showed lower performance in auditory-verbal tests and in executive functions compared to controls.

Twenty RE children and 24 controls were assessed concerning their oromotor function. The RE children had greater problems concerning tongue movements including articulation. A dichotic listening test was also performed in a subgroup showing poorer results in the RE group.

A simple classification is proposed with RE ‘pure’ as the main group and the frame for this study.

In conclusion, these investigations disclosed various abnormalities in children with RE, challenging the benign concept during the active phase. It is assumed that maturational factors comprise causal mechanism to the deviant findings, which probably successively will normalize.

Keywords: rolandic epilepsy, children, idiopathic focal epilepsy, magnetic resonance imaging, proton magnetic resonance spectroscopy, cognition, neuropsychology, oromotor performance, dichotic listening, hippocampus, classification

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[to Maria, 
Tove, Martin and Johan]
List of Papers

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


IV  Lundberg S, Frylmark A, Eeg-Olofsson O. Children with rolandic epilepsy have abnormalities of oromotor and dichotic listening performance (submitted).


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<th>Definition</th>
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<tr>
<td>ABPE</td>
<td>Atypical benign partial epilepsy</td>
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<tr>
<td>AED</td>
<td>Antiepileptic drug</td>
</tr>
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<td>BCECTS</td>
<td>Benign childhood epilepsy with centrotemporal spikes</td>
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<tr>
<td>Cho</td>
<td>Choline containing compounds</td>
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<tr>
<td>Cr</td>
<td>Creatine</td>
</tr>
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<td>CSWS</td>
<td>Continuous spikes and waves during slow-wave sleep</td>
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<td>CT</td>
<td>Computerized tomography</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>ESES</td>
<td>Electrical status epilepticus during slow sleep</td>
</tr>
<tr>
<td>FDG</td>
<td>$^{18}$F-fluorodeoxyglucose</td>
</tr>
<tr>
<td>Glx</td>
<td>Glutamine and glutamate</td>
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<tr>
<td>GTCS</td>
<td>Generalized tonic-clonic seizure(s)</td>
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<tr>
<td>HIBM</td>
<td>Hereditary impairment of brain maturation</td>
</tr>
<tr>
<td>$^1$H-MRS</td>
<td>Proton magnetic resonance spectroscopy</td>
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<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
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<td>MEG</td>
<td>Magnetoencephalography</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NAA</td>
<td>N-acetyl aspartate</td>
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<tr>
<td>OPL</td>
<td>Oropharyngolaryngeal</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts-per-million</td>
</tr>
<tr>
<td>RAVLT</td>
<td>Rey Auditory-Verbal Learning test</td>
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<tr>
<td>RD</td>
<td>Rolandic discharges</td>
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<td>RE</td>
<td>Rolandic epilepsy</td>
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<td>RS</td>
<td>Rolandic seizure(s)</td>
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<tr>
<td>SE</td>
<td>Status epilepticus</td>
</tr>
<tr>
<td>Shw</td>
<td>Sharp wave(s)</td>
</tr>
<tr>
<td>TLE</td>
<td>Temporal lobe epilepsy</td>
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<tr>
<td>VOI</td>
<td>Volume of interest</td>
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</table>
Introduction

Epilepsy syndromes are clusters of signs and symptoms customarily occurring together. Rolandic epilepsy (RE) is the most common focal epilepsy syndrome in the pediatric age group. Since it was described in 1958 (1), the syndrome has had a variety of denominations throughout the years. The name, proposed by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) 1989, is ‘benign childhood epilepsy with centrotemporal spikes’ (BCECTS) according to clinical and electro-encephalographic features (2). The prefix ‘benign’ is included in most of the synonyms (3) due to the excellent prognosis regarding the seizures which usually resolve at puberty as well as normalization of the EEG. However, several studies during the last decade have shown previous unattended cognitive deficits in children with RE, so that the favorable prognosis has been challenged. The definition and delineation of the syndrome has also been discussed over the last years.
Background

History
The name rolandic epilepsy alludes to the central sulcus of Rolando, named after the Italian anatomist Luigi Rolando (1773-1831). However, according to a historical review of the syndrome published by van Huffelen 1989 (4), this was an erroneous tribute to Rolando, who never contributed any scientific work concerning epilepsy. The first clinical description of RE can be ascribed to the Bavarian physician Martinus Rulandus (1532-1602). In one of his medical publications from 1597, he described the history of a 10-year-old boy presenting a ‘terrible epileptic disorder’ with brief seizures both day and night with convulsions of the left eye, mouth and arm, arrest of speech and a transitory paralysis of his left arm but without falling. Rulandus treated the boy with a concoction of lime tree blossom and brandy, and the boy was cured (!). The long-term outcome, however, is not told. This description of the seizure corresponds quite well to that occurring in RE and van Huffelen thus suggested the name Rulandic epilepsy instead of Rolandic epilepsy (4). However, the last-mentioned denomination has formed out to be the current one.

In modern times, the syndrome was not described and defined until the 1950s. The EEG features of what would later be called rolandic spikes or sharp waves (shw), were first reported by Y Gastaut in 1952, who called the discharges ‘prerolandique’ (5). Gibbs and Gibbs in the same year (6) and Gibbs et al. 1954 (7), entitled the spikes ‘mid-temporal’. The first accurate description of the electro-clinical syndrome was presented in 1958 by Nayrac and Beaussart (1) and this was followed by several other reports in the 1960s and 1970s. The most prominent authors in the delineation of this idiopathic focal syndrome were Gibbs and Gibbs (8, 9), Beaussart (10, 11), Lombroso (12), Loiseau (13-16), and Lerman (17, 18). In Scandinavia, Blom and Brorsson (19) and Blom and Heijbel (20-22) made important contributions and they also introduced the term “centro-temporal” and proposed the prefix “benign” (21).
Definition and prevalence

The current definition of RE is that of the Commission on Classification and Terminology of the ILAE 1989 (2), which is presented in full:

Idiopathic localization-related epilepsies are childhood epilepsies with partial seizures and focal EEG abnormalities. They are age-related, without demonstrable anatomic lesions, and are subject to spontaneous remission. Clinically, patients have neither neurologic and intellectual deficit nor a history of antecedent illness, but frequently have a family history of benign epilepsy. The seizures are usually brief and rare, but may be frequent early in the course of the disorder. The seizure patterns may vary from case to case, but usually remain constant in the same child. The EEG is characterized by normal background activity and localized high-voltage repetitive spikes, which are sometimes independent multifocal. Brief bursts of generalized spike-waves can occur. Focal abnormalities are increased by sleep and are without change in morphology.

Benign childhood epilepsy with centrotemporal spikes is a syndrome of brief, simple, partial, hemifacial motor seizures, frequently having associated somatosensory symptoms which have a tendency to evolve into generalized tonic-clonic seizure (GTCS). Both seizure types are often related to sleep. Onset occurs between the ages of 3 and 13 years (peak 9-10 years), and recovery occurs before the age of 15-16 years. Genetic predisposition is frequent, and there is male predominance. The EEG has blunt high-voltage centrotemporal spikes, often followed by slow waves that are activated by sleep and tend to spread or shift from side to side.

This definition does not take into consideration several new aspects of the syndrome, which have been reported and discussed over the last decade, as neuropsychological abnormalities and different expressions of the syndrome. For instance, there is common agreement that the focal (partial) seizures quite often are accompanied by some impairment of consciousness. Consequently, there have been somewhat different inclusion criteria for RE amongst epileptologists when studying populations of children with epilepsy. This has resulted in a varying range of prevalence figures.

The prevalence figures of RE in childhood epilepsy populations comprising children up to 15/16 years, excluding neonates are:

Heijbel et al. 1975 (23) 15.7 % and Sidenvall et al. 1996 (24) 17.4 % (both Umeå, Sweden); Panayiotopoulos in Athens, Greece 1989/1993 (25, 26) 15.3/14.6 %, and Larsson and Eeg-Olofsson, Uppsala, Sweden 2001 17.6% (personal communication).

In children between 5 to 14 years, Cavazzuti, Italy 1980 (27) reported a prevalence of 23.9 % and Panayiotopoulos (25, 26) 24.6 %. Doose and Sitepu studied children aged 0 to 8 years in Northern Germany 1983 (28) and found a prevalence of 8 %. A slight male predominance is reported (16, 29, 30).
Seizures and other clinical manifestations in RE

The seizures in connection with RE are called rolandic seizures (RS). The onset occurs between the ages of 3 and 13 years, in 76% between 5-10 years, with a peak at 9 years (18). Seizures only during sleep are most frequent (70-80%), in the majority in nocturnal sleep, typically arising shortly after the child has fallen asleep or before awakening in the morning. Seizures exclusively when awake are less frequent (10-20%) (18), and seizures when both awake and during sleep occur in approximately 15% (18) to 23% (16).

The first seizure is typically observed by the parents as GTCS during sleep, and this may bring the family to the hospital. The genuine RS is a focal seizure, which originates from the rolandic area. The consciousness is most often unimpaired but may be blurred, which can be difficult to evaluate for observers. An appropriate description of the seizure semiology is crucial for a correct diagnosis.

The characteristic features of a RS includes:

**Hemisensory symptoms** as paraesthesias with numbness and tickling sensations from the face, mouth, lips, inner cheek, tongue, gum and throat and **hemimotor symptoms** from the face, lips and mouth which consists of brief, rhythmic contractions. The hemifacial symptoms occur in about a third of the children (31). Both hemimotor symptoms and paraesthesias may also progress to the arm ipsilaterally but the leg is very rarely involved.

**Oropharyngolaryngeal (OPL)** symptoms are classical RS manifestations and occurs in more than 50% (31). The symptoms are mainly motor but may also be sensory. They are described as guttural, moaning, gurgling, chuckling, grunting, roaring, gasping, and wheezing sounds. The child may describe a feeling of strangulation or choking. However, usually the child is unconscious, and the described sounds will often draw the attention of the parents to the child in the bedroom.

An associated very characteristic symptom is **speech arrest**, which occurs in more than 40% of the seizures (12, 15, 17). The child is conscious but becomes frustrated because of the inability to speak, except for producing some OPL sounds. This can be explained as an ictal anarthria, i.e. loss of power and co-ordination to articulate words (12, 15, 17, 31).

**Hypersalivation** is also a common ictal phenomenon occurring in about one third of the children (31). The drooling is thought not only to be a consequence of swallowing difficulties but also a genuine sialorrhoea as an autonomic ictal manifestation which, according to Lüders, probably is “due to involvement of the superior bank of the sylvian fissure” (29).

The focal seizure has a strong tendency to **secondary generalization**, which most often occurs during sleep. Thus, a focal seizure onset will often not be
witnessed. Secondarily generalized seizures are reported in one to two thirds of the children.

A so called Todd’s paralysis, i.e. a postictal paralysis most often of one arm, has been reported in 7-16 % (15, 32, 33).

The frequency of RS is highly variable irrespective of treatment. Some authors include children with only one verified RS in their series (16, 17) which is strictly not in accordance with the definition of epilepsy. It is quite common that seizures occur in clusters for some days up to a few weeks followed by a seizure-free interval of several months. In 10-20 % the seizures may be frequent and resistant to treatment (18).

Precipitating factors are in correspondence with epilepsy in general (e.g. sleep deprivation, fatigue, minor illness, fever), but most often the RS occur unprovoked. Focal status epilepticus in children with RE is reported by a few authors (31, 32, 34-38).

EEG in RE

The interictal EEG findings are essential for the diagnosis of RE. The hallmark is the rolandic spike or sharp wave (shw) with a characteristic morphology. The shw is also called ‘benign focal shw’, referring to the absence of corresponding (cortical) morphological lesions and are also described in other idiopathic epilepsies (39), as well as occurring in individuals without seizures (40). By definition, the distinction between a spike and a shw is the duration of the discharge. A spike has a duration less than 70 ms and a shw above 70 ms but not exceeding 200 ms. However, this discrimination is not of any practical importance for the epileptologist when considering RE, and the terms are most often used interchangeably.

The morphology of the shw can be described as follows: A low amplitude positive wave is generally followed by the characteristic high negative wave with a peak amplitude often exceeding 200 µV, but this can be smaller or markedly higher. The average amplitude has been estimated to 160 µV (41). Then three positive or negative slow waves follows and this constitutes the so-called “five-component shw” according to Doose (39). However, the shape can be altered depending on localization, age, tendency to generalization, and by sleep activation.

The shw constituting the electrographic sign of RE will in the following be called rolandic discharge (RD).
Figure 1. Interictal EEG of a 6-year-old girl (case 18) during drowsiness. The EEG was performed four months after onset of characteristic left-sided RS, which were initially frequent during several days until she was successfully treated with carbamazepine. The EEG shows typical RD in the right centrotemporal area (phase reversal C4), and contralateral synchronous RD of lower amplitudes.
Figure 2. Interictal EEG of a 9-year-old girl (case 14) during drowsiness. She had RE onset at age 7 years and was successfully treated with valproate. Frequent RD in clusters are seen with typical morphology with maximum at electrode C3 on the left side.
The *localization* of the RD is classically a horizontal dipole with maximal electronegativity in the centrotemporal (midtemporal) area and with the electropositivity in the frontal regions (42, 43). It may also be located in the centro-parietal, fronto-central or centro-occipital areas. The localization of RD in general is age dependent with parieto-occipital foci usually occurring before the age of four while centrotemporal (midtemporal) RD peak around the age of eight (6, 44). Drury et al. (45) found RD outside the centrotemporal area in 21% of children with a typical history of RE and stated that the most important feature is the monomorphic shw and not the location. The RDs are located unilaterally in around 60% and bilaterally in around 40% with the foci tending to shift from side to side asynchronously (18) and synchronously (12, 29). There is a tendency of the RD to appear in clusters with a rhythm of 1.5 to 3 Hz (46). They typically increase in frequency during drowsiness and sleep and tends to become bilateral, usually with unchanged morphology (20). In approximately 30% of the children with RE, shw appear only in sleep (12, 20). This emphasizes the importance of getting a sleep EEG that usually is obtained by sleep deprivation. Activation with hyperventilation or photic stimulation does not influence the frequency of discharges. Lerman and Kivity (17) found no correlation between the intensity of the discharges and frequency, length or duration of the RS.

The *background* activity should by definition be normal. However, there are some reports of focal (47, 48) or bilateral (49) episodic slow activity.

Several *ictal recordings* in RE have been reported since the first one of Dalla Bernadina 1975 (50-54) and there are also some reports when awake (18, 50, 55-57). The semiology has been described as typical of RS with EEG showing fast, repetitive spikes from the centrotemporal (midtemporal) area unilaterally, with or without preictal decrement and postictal slowing of activity, respectively.

**Cerebral lesions and RE**

RE has been reported in children with cerebral lesions with different aetiologies and clinical presentations. Blom et al. (21) described in their series of 40 children two with slight hemiparesis. Santanelli et al. (58) reported three patients with electro-clinical findings in accordance with RE. However, CT scans showed agenesis of the corpus callosum, a lipoma of the corpus callosum, and congenital toxoplasmosis, respectively. Lerman and Kivity (17) found three of 100 children with RE suffering from cerebral palsy and another from microcephaly. Lerman considered RE in the children described in these reports as “fortuitously superimposed or ‘grafted’ on to an injured brain,” and the prognosis concerning RE as good as in normal children (18).
Shevell and coworkers described five children with suggestive RE where MRI or CT revealed mass lesions with variable locations (59). Stephani and Doose (60) reported a girl with severe head trauma in the neonatal period resulting in spastic tetraplegia, mental retardation and simple focal seizures occurring from the right orofacial region from 28 months of age. At the age of five she had typical RS with a benign course. As her sister showed RD on EEG, the authors concluded that the proband did not just have a ‘phenocopy’ due to the brain lesion. Thus, the genetic predisposition of RD underlying RE, can be involved also in the pathogenesis of seemingly pure symptomatic epilepsies. Gelisse et al. (61) reported enlargement of the lateral ventricle in five children of whom two had shunted hydrocephalus.

Other structural lesions exclusively revealed by MRI will be presented in the following.

Neuroimaging in RE

Neuroimaging of idiopathic epilepsies has been regarded as superfluous due to the good prognosis concerning seizure outcome according to many authors (10, 11, 62, 63). However, it is recommended if any atypical electroclinical features are found (55, 61). MRI is today the imaging method of first choice for identifying the structural basis of epilepsy, and the technique is still improving. Prior to the MRI era or in the early years of MRI, i.e. mid 1980s, CT was the only imaging technique that was available. Systematic CT studies of benign focal epilepsy have not been performed to my knowledge. However, CT has been used now and then in RE series in selected cases excluding gross morphological abnormalities. Because of its availability, CT is nowadays used only in the very acute or initial phase of epilepsy to exclude tumor or haemorrhage.

Magnetic Resonance Imaging (MRI)

Over the last years, a few case reports of MRI studies in children with RE have been reported. Gelisse et al. (64) presented a 10-year-old boy with clinically typical RE, the MRI disclosing a very marked right sided hippocampal atrophy. However, because of absent clinical correlates and no apparent cause to the atrophy, they concluded that the seizure disorder could not be ascribed to this abnormality. Cortical dysplasia has also been found in children with typical RE (65, 66). Shet et al. (65) reported cortical dysplasia in the suprasylvian region, which was regarded as an incidental finding. In a case of unilateral opercular macrogryia (unspecified location), this malformation was supposed to provide an epileptogenic zone causing rolandic discharges (66).
Proton Magnetic Resonance Spectroscopy (\(^1\)H-MRS)

\(^1\)H-MRS provides a non-invasive means of investigating the biochemistry in various tissues. The brain has been one of the most studied organs and the clinical applications are mainly brain tumors, degenerative or neurometabolic brain disorders and epilepsy. The application of \(^1\)H-MRS, in attempt to delineate the epileptogenic zone in epilepsy, has mainly concerned presurgical evaluation of temporal lobe epilepsy (TLE), but it has also been performed in extra-temporal epilepsies. \(^1\)H-MRS, however, is not used in common clinical routine. In research, \(^1\)H-MRS studies in focal idiopathic epilepsies including RE have so far not been performed.

\(^1\)H-MRS background

\(^1\)H-MRS, in contrary to MRI, does not primarily produce an image but spectra showing peaks of metabolites. The spectra are achieved by excitation of protons in a strong magnetic field by a specific radio frequency (RF) pulse. The protons then emit a RF signal of a characteristic resonance frequency, which is dependent on the chemical environment, i.e. in which molecule the proton finds itself. The differences of the resonance frequencies are referred to as ‘chemical shift’ and are presented along a horizontal axis (x-axis) plotted in ‘parts-per-million’ (ppm). The area under the peak represents the relative concentration of protons giving origin to the peak signal. Mainly two localization methods are used: STEAM (Stimulated Echo Acquisition Mode) and PRESS (Point-Resolved Spectroscopy), both providing localization in three dimensions. These methods can be applied to two spectroscopic techniques; single voxel and multiple voxels or chemical shift imaging.

The main metabolites in gray and white matter detected by \(^1\)H-MRS in epilepsy assessments are:

- **N-acetyl aspartate** (NAA) and N-acetyl aspartyl-glutamate (NAAG) (occurring at 2.02 ppm) are often mentioned as total NAA (tNAA). NAA is considered as a marker of neuronal function and is confined to neurons and neuronal processes both in gray and white matter. Decreased signal intensity indicates neuronal loss or neuronal dysfunction. The exact functional role of NAA is still not completely understood.

- **Creatine (Cr) and phosphocreatine** (3.03 ppm) (total creatine; tCr) are involved in the generation of ATP. The concentration is considered as quite stable but deviations are observed in tumors, stroke and in some metabolic diseases.

- **Choline containing compounds** (Cho) (3.21 ppm) is required for synthesis of acetylcholine and of phosphatidylcholine, a major constituent of membranes. It is also considered as mainly stable, though alterations can be observed in neoplasms and in ischemic and neurometabolic disturbances.
Glutamate (Glu) and glutamine (Gln) (together termed Glx; 2.2-2.4 ppm). Glu is the main excitatory amino acid in human brain and Gln its precursor and storage form. To obtain a satisfying resolution, a short echo time acquisition is required. Theoretically, measurements of Glx would contribute in evaluating epilepsy, however, up to now few studies have been published using Glx as an epileptic marker (67-74).

The metabolites are measured quantitatively or qualitatively. In qualitative studies, NAA/Cr or NAA/ Cr + Cho ratios are most often used as indicators of neuronal function. As mentioned, the most studied individuals with epilepsy are those with intractable TLE. There is a voluminous literature concerning TLE in adults, and in some reports children are included. Few studies concern solely children (75-80). The main issues are lateralization and a more thorough localization of the epileptic focus and prognosis of TLE, which is mostly post-surgery. There is an unanimous opinion that $^1$H-MRS provides a sensitive tool of detecting neuronal dysfunction by measurement of relative or absolute concentrations of the NAA in the temporal lobes including hippocampi. This also includes dynamic properties of NAA levels. These can be below normal level even contralaterally to the TLE. Cendes et al. (81) and Hugg et al. (82) have shown, mainly in adults with TLE, a normalization of NAA ratios on the opposite side after successful epilepsy surgery. Cendes et al. hypothesize that it is the seizure activity itself that lowers the NAA. However, Li et al. (83), examining individuals with focal epilepsies successfully treated with antiepileptic drugs (AED), did not find recovery of the NAA ratios. They concluded that absence of seizures is not necessarily coupled to NAA improvement.

There are some $^1$H-MRS studies in normal children with the purpose of studying the age development of the metabolites. Van der Knaap et al. (84) studied predominantly white matter with single-voxel technique and found the most rapid increase of NAA ratios to occur during the first three years of life. Kadota et al. (85), used multivoxel $^1$H-MRS to calculate NAA/Cho ratios in the human cerebrum. However, individuals in the first four years of life were not included. The results demonstrated a rapid increase of the ratio in white matter during the first decade. In contrast, in isocortical gray matter the ratio showed a gradual decline with age. Choi et al. (86) compared allocortex, i.e. mainly hippocampal formation, and isocortex (neocortex) in the frontal and parietal lobe in 30 healthy children aged 3-14 years with a single-voxel (5 in allocortex and 7.2 ml in isocortex). They found a lower NAA/Cr ratio in allocortex compared to isocortex, but no significant hemispheric asymmetry in allocortex and no significant correlation between age and metabolic ratios in either allocortex or isocortex.
Positron Emission Tomography (PET)

Very few functional neuroimaging studies utilizing PET have been performed in children with idiopathic partial epilepsy. De Saint-Martin et al. (87) reported a longitudinal study of a child with RE using $^{18F}$-fluorodeoxyglucose (FDG) PET. They found a bilateral increase of glucose metabolism in the temporal opercular regions interictally during the ‘active’ phase of the epilepsy. Van Bogaert et al. (88) using FDG-PET in eleven children with RE could not demonstrate any interictal side differences in glucose metabolism.

Neuropsychological evaluation in RE

In earlier studies of RE, the children were described as ‘neurologically normal’ because the condition was considered ‘benign’. In some larger studies, children with behavioral and neuropsychological problems were excluded a priori (11) and few systematic neuropsychological studies have been published (89). Some remarks of behavior and learning problems have been reported, but these were attributed to psychosocial factors, or to adverse effects caused by treatment with barbiturates (17, 18). Panayiotopoulos (31) states in his comprehensive survey of RE: “The general view is that children with RS are not different from other normal children regarding intelligence, school performance, behaviour and development. This is also my view.”

Nevertheless, this opinion has been questioned over the last decade by several authors, who can be divided into two groups: those who ascribe the cognitive impairment to ongoing epileptic discharges, i.e. RD, and those who attribute it to the basic cerebral dysfunction responsible for the epileptic manifestation. An Italian group (90, 91) studied the influence of epileptic discharges in EEG on cognitive function and attention in children with RE by sub-grouping them into left, right and bilateral discharges. They found that cognitive impairment “appears to be to some extent related to the EEG focus.” The worst scores were found in the group with bilateral discharges (90). In a later study, they confirmed a significantly lower score in RE children with a right sided focus or bilateral foci (91).

Binnie and Marston (92) studied 10 children with ‘rolandic spikes’, and seven of them had seizures in accordance with RE. In connection with an EEG registration they performed a test of short-term memory for spatial material. Four of the seven children showed a significantly higher error rate in trials accompanied by EEG discharges. They concluded that the occurrence of ‘rolandic spikes’ might be accompanied by transient cognitive impairment (TCI). This observation has been cited quite often and has established a still ongoing discussion as to whether ‘interictal’ discharges can affect brain activities expressed as TCI, and consequently should be treated with AED.
Deonna et al. (93) studied 19 children with typical RE. They found that a proportion of the children showed mild and transient cognitive difficulties during the ‘active’ phase of their epilepsy. These difficulties were probably related to EEG activity, and they concluded that a trial of AED on children suspected to have cognitive or learning difficulties was advisable. Weglage et al. (94) investigated 40 children with ‘centrotemporal spikes’, 20 with seizures and 20 without seizures, i.e. 50 % did not have RE. The performance of these children regarding visual perception, short-term memory and IQ was significantly impaired compared with matched controls. They also found a correlation between the number of spikes and deficits in IQ, suggesting that AED should be tried even in children without seizures.

Staden et al. (95) reported impairment of language skills in 13 of 20 children with RE, suggesting the cause to be an interictal dysfunction of the perisylvian language area.

In a prospective study, Baglietto et al. (96) investigated nine children with RE and with “marked activation of interictal epileptic discharges during sleep” compared with matched controls. The patients were seizure-free during the study period. A test battery revealed significantly poorer results in the RE children concerning visuospatial short-term memory, visuomotor coordination, picture naming and fluency, attention, and cognitive flexibility. At remission of the discharges, both spontaneously and after treatment with diazepam, all patients showed normalization of the results, and also an improvement of IQ. The authors proposed a brief period of diazepam treatment in order to shorten the time for recovery from the interictal discharges, thereby improving the neuropsychological condition.

In a retrospective study, Yung et al. (97) reported 56 children with centrotemporal spikes on EEG and seizures compatible with RE. Interestingly, they found three children with language delay and regression. One child had abundant bilateral independent shw during sleep but did not fulfill the criteria for continuous spikes and waves during slow-wave sleep (CSWS). Another child had a sister with CSWS. However, neither the second child nor the third one had EEG features of CSWS. Behavioral problems and/or learning disabilities were found in 14 % of the RE children and mild to borderline intellectual dysfunction in 12 %. However, the authors admitted that the study represented a skewed population.

Oromotor disturbances in RE

The characteristic semiology of RS comprises OPL symptoms including speech problems, hypersalivation or sialorrhea and rhythmic hemifacial contractions. These ictal events are normally of short duration and do not harm the children otherwise in their daily living apart from the seizure itself. However, prolonged and severe oromotor dysfunction has been reported in
RE children with duration from hours to several weeks. Fejerman and Di Blasi (34) reported two children with RE and partial status epilepticus (SE) presenting continuous hemifacial twitching, dysarthria or anarthria and sialorrhea, one of them also having swallowing difficulties. The symptoms lasted for five days and one month respectively. Since then, similar oral dysfunction symptoms attributed to partial SE in children with RE have been reported (35, 37, 38, 98). There are also case reports of transient oromotor deficits, most often correlated with abundant interictal epileptic activity but not defined as partial SE (36, 87, 99-101). The RDs are almost exclusively bilateral, which seems to be necessary for these symptoms to occur (87, 99, 100).

Some of the reports of RE with oromotor dysfunction discuss these cases in terms of a ‘functional anterior opercular syndrome’ (36, 87, 98, 102-104), also designated Foix-Marie-Chavany syndrome.

Family history and genetics in RE

Idiopathic or ‘primary’ epilepsies as RE favour a genetic origin. In 1964, Bray and Wiser (105) studied the families of 40 index cases with ‘temporal-central’ spikes, i.e. RD, with or without seizures. The prevalence of RD was 36% in siblings and children compared to 2% in controls. They concluded that the occurrence of RD follows an autosomal dominant mode of inheritance. In 1975, Heijbel et al. (106) obtained almost the same results when evaluating the families of 19 children with RE. Eleven of 32 siblings (34%) showed RD in wake or sleep recordings, and five of them had generalized seizures. They concluded that the result indicated an autosomal dominant gene with age-dependent penetrance responsible for the EEG trait. Degen and Degen (107) studied 69 siblings of 43 children with RE and/or RD and found RD only in four (5.8%) of the siblings which is close to around 3% found in normal children age 3–14 (40). Despite this low prevalence, they agreed to the preceding author’s opinion of inheritance. Doose et al. (108) proposed a multifactorial inheritance of the EEG trait, which is regarded as a genetic marker of not only RE but also of other epileptic and non-epileptic disturbances. This concept is denominated ‘hereditary impairment of brain maturation’ (HIBM). In 1998, Neubauer et al. (109) found a linkage to chromosome 15q14 in 22 families with 54 members having RD and 43 of these having RS. It was concluded that either the alpha 7 AChR subunit gene or another closely linked gene are implicated in pedigrees with RD and that the trait is genetically heterogeneous. So, the gene localization of RE is still to be determined.
Treatment of RE

Treatment of RE is optional and may be performed only from psychological and practical reasons (110, 111). The decision of treatment, which is restricted to pharmacological alternatives, has to be properly discussed with the child and the family including presentations of pros and cons. One has to consider that seizures normally are infrequent, brief, and most often nocturnal, thus having a minimal influence on the daily life of the child. Furthermore, pharmacological treatment, i.e. AED, does not influence the prognosis of RE and, according to some authors, does not easily efface the RD (10). However, other authors have proposed ‘treatment of the EEG’, i.e. to treat interictal activity in order to minimize the risk of minor cognitive impairment (92-94, 97, 100).

If treatment is advised, there are several alternatives of AEDs, and literally the same as in other focal epilepsies. Carbamazepine is an effective and mostly well tolerated drug, but may in exceptional cases aggravate seizures (37, 104, 112-114) or induce epileptic negative myoclonus (115, 116). A similar drug is oxcarbazepine, which also has been reported to exacerbate seizures (117). Sulthiame has been used mainly in Europe, and it is a well tolerated and an effective alternative in the treatment of RE (118, 119). Additionally, marked improvement of the EEG with normalization in the majority of cases has been found (120, 121). Moreover, valproate, benzodiazepines, phenytoin, phenobarbiturate, lamotrigine and gabapentin have also been used in the treatment of RE. A small percentage of children with RE may have refractory seizures (10, 33, 122).

Discontinuation of treatment is generally recommended if the patient is seizure-free for one or two years (18, 31, 55, 123).

Prognosis of RE

A hallmark of RE is that seizures remit before or during puberty, at the latest at 16 years of age, usually between 9 to 12 years (10, 16, 124). In a meta-analysis of 20 reports comprising 794 RE children, Bouma et al. (30) found that the mean duration of active RE was less than three years. Most of the children had only few seizures and were in remission by the age of 12 or 13 years. They concluded that early prediction of seizure outcome in a new RE patient cannot be given with certainty because of the fact that the selected studies showed a highly heterogeneous methodology, and that all were retrospective with biased cohorts. One of the 13 selected study cohorts consisted of 168 patients in a follow-up study by Loiseau et al. (16). They found a relation to age at onset of RE, i.e. the earlier the onset, the longer the active period. Three of the patients had experienced further seizures, all of them GTCS, after the age of 18 years. The authors stated that the relative risk of
such late occurring seizures was 10-fold in the RE population. Other studies have also described a few individuals with sporadic GTCS in adulthood after remission of RE (11, 21, 31, 122), and the risk has been estimated to less than 2 % (16, 31). Focal seizures in the follow-up into adulthood are extremely rare (16, 125, 126), and only one case with relapse of RS has been reported (126).

The prognosis of social adaptation, school achievement and professional activity appears to be good according to long-term follow-up studies (16, 122, 125). Loiseau et al. (16) put the phrase “for unknown reasons, social level seems to be even higher than for nonepileptic people.”

The normalization of EEG occurs usually later than the clinical remission. Aicardi mentioned the average interval to be two years (127).

Benignity of RE and atypical RE
RE has been considered and also denominated as ‘benign’, mainly according to the excellent prognosis of RS and the disappearance of RD. Several authors have, principally because of the occurrence of abnormal neuropsychological findings (see previous), questioned the benignity of RE. There has also been some case reports of intractable seizures in children with possible RE (57) as well as of morphological abnormalities (59, 64-66). Recently, some authors proposed that there are different phenotypes within the RE group, and the children were separated into ‘typical’ and ‘atypical RE’ (35, 128). The prognosis, especially concerning the neuropsychological outcome, has been found less favorable in the group with the ‘atypical’ form (35, 128). These observations stress the necessity to make a proper delineation of RE rendering it easier to perform adequate studies of the syndrome.

Relations to other idiopathic epilepsy syndromes in childhood
RE belongs to the idiopathic focal epilepsies also including benign partial epilepsy with affective symptoms (‘benign psychomotor epilepsy’) and benign childhood occipital epilepsy. The last-mentioned consists of both early onset benign childhood epilepsy with occipital paroxysms or Panayiotopoulos syndrome, and the more rare late onset Gastaut type idiopathic childhood occipital epilepsy (129). RE and Panayiotopoulos syndrome have specific semiologies, but have in common that they are age-related, have a favorable seizure outcome and that EEG shows the typical benign focal shw of RD type, though the localizations are different. Moreover, these shw are also seen in acquired epileptic aphasia or Landau-Kleffner syndrome (LKS) and in the syndrome continuous spikes and waves during slow-sleep (CSWS) or
electrical status epilepticus during slow-sleep (ESES) (130). In these syndromes, characterized by behavioral, cognitive and language disturbances, seizures are absent in up to 30%. RE may exceptionally be transformed into CSWS (35), sometimes precipitated by carbamazepine (37). Atypical benign partial epilepsy (ABPE) was reported by Aicardi 1982 (131) also called pseudo-Lennox syndrome, and is characterized by generalized minor seizures and focal shw similar to RD. The seizure outcome is favorable, but mental deficits are common (132). There is a broad overlap with CSWS/ESES and LKS (35, 130, 132). Doose and Baier (108) proposed the hypothesis of HIBM in view of the common benign focal shw or RD, and the clinical overlap of the described syndromes. This concept includes also seizure-free individuals with behavior disorders and slight mental retardation with RD. In this view, RE, and especially RE ‘pure’ is in the very benign end of a spectrum of clinical entities with a common complex pathogenetic background.

Additionally, Scheffer et al. (133) reported a rare syndrome, autosomal dominant rolandic epilepsy with speech dyspraxia, which has electro-clinical features resembling RE.

Fig 3 presents schematically the syndromes described with their relations to RE and the difficulties of making exact delineation between syndromes. The figure includes ‘atypical RE’ which is a diffuse entity discussed in the previous chapter.
Figure 3. A schematic presentation of RE, related epilepsies, and conditions similar to RE. The size of the circles does not represent the prevalence or proportions between the conditions.

LKS: Landau-Kleffner syndrome; CSWS: continuous spikes and waves during slow-sleep; ESES: electrical status epilepticus during slow-sleep; ABFE: atypical benign focal (partial) epilepsy.
Aims of the study:

Over the last years, some reports describing RE have included individuals characterized as ‘less benign’, ‘atypical’ and even ‘malignant’. In other reports the presence of cognitive dysfunction has been highlighted.

The general aim of this study was to investigate children with electro-clinically typical RE without any obvious signs of neurological or psychological disturbances (RE ‘pure’) using various methods.

The specific aims were:

1. to reveal the presence of morphological brain abnormalities by magnetic resonance imaging (MRI) (paper I)

2. to reveal the presence of metabolic disturbances or asymmetry of the hippocampal regions by proton magnetic resonance spectroscopy ($^1$H-MRS) (paper II)

3. to reveal any cognitive dysfunction by neuropsychological assessment using a test battery measuring auditory-verbal, visuo-spatial and executive functions (paper III)

4. to reveal any speech defect by orofacial motor and sensory tests and any auditory abnormalities by dichotic listening test (paper IV)

5. to discuss the delineation of RE (paper V)
Subjects

All children with RE were recruited from our epilepsy outpatient clinic at the University Children’s Hospital, Uppsala, Sweden, and all were living in the county of Uppsala, with a population of about 60,000 children. They were asked for participation in the different studies separately. Informed consent was obtained from the children and their families in Study II, III and IV. Applications were presented to the Human Ethics Committee of the Medical Faculty, Uppsala University, and these were approved.

An overview of the participants in Study I-IV is presented in Table 1 and 2. Thirty-eight children, 18 girls and 20 boys, with a seizure onset between 3 and 11 years (mean 6.8, median 7) participated in at least one of the studies (I–IV). Three children had participated in all four studies, five in three, eleven in two, and 19 in one study. Two pairs of siblings were included (cases 9 + 15 and case 12 + 13). One child was left-handed (case 1), and one was ambidextrous (case 14).

The RE diagnosis was evaluated and confirmed for each child by the author, mainly by personal consultation or, in a few cases, after having read the hospital record of the child. Additional information was obtained when needed. All children had undergone at least one EEG including sleep recording. The electro-clinical features of RE according to the ILAE criteria (2) had to be fulfilled. Some of the children included in Studies I–III were excluded in Study IV as they had been seizure-free with or without AED for five years, i.e. they did not have ‘active’ epilepsy.

The seizure frequency was mainly low for all children except for some children who had frequent seizures for a few days in the initial phase. No one had had status epilepticus. Eight children had never been treated with AED. Sixteen had been treated with one AED, nine with two, four with three and one child with four AEDs usually as monotherapy but also in combinations. Thus, at any time 23 children had been treated with carbamazepine, 19 with valproate, four with sulthiame, two with nitrazepam and two with ox-carbazepine.
Table 1. Number of participants and overlap in Study I–IV.

<table>
<thead>
<tr>
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Table 2. RE children and their participation in Study I–IV.

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<th>Study II 1H-MRS MRI</th>
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M: male; F: female; MRI: magnetic resonance imaging; 1H-MRS: proton magnetic resonance spectroscopy.
*Subjects participated in Study II although their results were rejected owing to suboptimal quality of the spectra.
# Number of studies in which the individual case participated.

Total RE: 18 13 13 17 20
Controls: 0 15 13 17 24

30
Study I

The origin for this study was a girl with typical RE with recurrent typical seizures resistant to common AED (case 1). A MRI examination disclosed obvious hippocampal asymmetry. This finding encouraged us to MRI examine a consecutive series of children with RE as part of the clinical evaluation.

Eighteen children with electro-clinically characteristic RE, 9 girls and 9 boys, with an age range of 6–12 years (mean 9.2, median 10) were included. The age at seizure onset was between 3 and 10 years (median 6 years), and the mean duration of RE was 2.3 years. All children had been seizure-free more than one month prior to the examination and all but one child were treated with AED (carbamazepine or valproate). One girl had suffered from one typical febrile seizure episode in infancy (case 8). They were all neurologically and mentally normal. Two children were initially considered as left-handed (case 1 and 14), one of them were re-evaluated as being ambidextrous (case 14).

There were no controls included in the study.

Study II

The results of Study I justified further studies of hippocampus in children with RE. Seventeen children were recruited mainly from the Study I population, 11 girls and 6 boys with an age range of 8–14 years (mean 11.3, median 11). High spectral quality bilaterally was obtained in 13 children. In the remaining four children this was not achieved due to movement artifacts, and so they were excluded. Consequently the study group comprised 9 girls and 4 boys, aged 8–14 years (mean 11.7, median 12). The onset of RE was between 4 and 11 years (median 7) and duration of epilepsy was between 2 and 8 years (mean 4.4). All children were neurologically and mentally normal and all were right-handed. One girl had had one typical febrile seizure in infancy (case 8). Six of the children were treated with AED (valproate, carbamazepine or sulthiame), four children had been without treatment for at least one year, and three children had never been treated. Three children had inactive epilepsy, i.e. they had been seizure-free for up to five months beyond the five years (cases 2, 6 and 10). In the other patients, the interval between the 1H-MRS and the latest seizure episode was at least one month.

The control group consisted of 22 children. Due to suboptimal spectral quality, seven were excluded. Of the remaining 15 children, there were 8 girls and 7 boys, aged 8–14 years (mean 11.1, median 11). Two children declined to participate in a MRI examination. Twelve of the 22 children had participated as controls in Study III, where they had been matched for age, sex and school performance. The additional ten had been matched for age and sex. All were healthy and with normal psychomotor development, and there was no history of febrile or any other seizures.
Study III

The study was initiated after Study I. Seventeen children, 7 girls and 10 boys, aged 7–14 years (mean 9.9, median 10.5) were included consecutively in the study. Seizure onset was between 3 and 10 years of age (mean 6.3, median 7) and the mean duration of RE was 3.9 years (median 3). All children were neurologically and mentally normal. One girl had suffered from one typical febrile seizure episode in infancy (case 8). Twelve children were treated with AED (valproate or carbamazepine) at the time of investigation. All children had Swedish as their native language.

A control group of 17 children mainly classmates to the RE children were enrolled in the study. They were matched with respect of sex, age and estimated intelligence according to evaluations of their teachers and parents. Twelve of these children did also participate in Study II and nine participated in Study IV.

Study IV

Twenty children with typical RE, 11 girls and 9 boys, age range 8.2–14.6 years (mean 10.5, median 10.2) were included. The seizure onset ranged from 3 to 11 years (mean 7.1, median 7) and the duration of RE at the time of assessment between 1 to 9 years (mean 3.5, median 2.7). Twelve children were treated with AED (carbamazepine, valproate or sulthiame) at the time of investigation and two children had previously been treated with AEDs. All were neurologically and mentally normal. One boy had slight speech problems, otherwise no speech, language or swallowing problems were known. One girl was left-handed (case 1) and four children had a history of one to three typical febrile seizures (case 8, 27, 29 and 35).

The control group consisted of 24 children, 14 girls and 10 boys, with an age range of 8.2–14.4 years (mean 11.0). They were mainly age- and gender matched schoolmates to the RE children and without known speech, language, hearing or learning problems. Two children were left-handed. Nine control children were the same as in Study III. All children had Swedish as their native language.
Methods

Study I

MRI was performed with a 1.5 Tesla imager (Gyroscan NT, Philips, Best, The Netherlands) at the Neuroradiological department, University Hospital, Uppsala. Sedation or general anesthesia was not used. The sequences used were according to the established ‘epilepsy program’:

- Sagittal T1-weighted spin echo images, 5-mm sections, 0.5-mm interslice gaps.
- Oblique axial images in the plane of the long axis of the hippocampus. Proton density- and T2-weighted spin echo images 4-mm thick, 0.4-mm interslice gaps. Turbo inversion recovery images 2.0-3.5 mm thick, no interslice gaps.
- Oblique coronal images in a plane perpendicular to the long axis of the hippocampus, no interslice gaps. T2-weighted turbo spin echo images 2.5 mm thick, turbo inversion recovery images 2.0-3.5 mm thick.
- The field of view varied according to head sizes, and the matrix was most often 205 x 256.

One experienced neuroradiologist (R. Raininko), who neither had knowledge of the clinical histories, nor the EEG results, reviewed the images visually.

A follow-up MRI was performed in six children after one to three years and reviewed by the same observer.

Study II

The study was performed on the same 1.5 Tesla MR system as in Study I, applying the standard quadrature transmitter-receiver birdcage head coil. No sedation or general anesthesia was used.

T1-weighted transverse, sagittal and coronal spin echo images were used to position the volume of interest (VOI). The VOI, or single voxel, was a rectangular box of dimensions 40 x 20 x 20 mm³ (16 ml), which was individually adjusted to cover most of the hippocampus, and to minimize partial volume effects with other tissues. The resulting VOI consisted mainly of the hippocampus and small portions of the perihippocampal brain tissue and
Cerebrospinal fluid. Proton spectra of both hippocampal areas were recorded with use of a PRESS sequence (TR/TE = 2000/32 ms, 256 accumulations, 1024 points, spectral bandwidth 1000 Hz), which also included unsuppressed water reference scans for neurochemical quantitations. The acquisition time for each hippocampus was 8 minutes and 40 seconds. The total time required for the 1H-MRS measurements was around 45 minutes.

Data processing

Automated quantification of absolute metabolite concentrations was accomplished by LCModel (linear combination of model spectra of metabolite solutions in vitro) (134), a user-independent frequency domain fitting program. The method uses the experimentally determined spectral pattern of each metabolite without further analysis.

Concentrations are calculated as mmol/liter (mM) VOI, and are not corrected for residual T1, T2 relaxation effects and CSF contributions.

The identified metabolites were:

- Total N-acetyl aspartate (tNAA), i.e. the sum of N-acetyl aspartyl-glutamate and NAA.
- Total creatine (tCr), i.e. the sum of creatine and phosphocreatine.
- Choline-containing compounds (tCho).
- Glutamine/glutamate complex (Glx).

The concentration ratio (R) tNAA/tCr was calculated for the left (R_L) and right (R_R) hippocampal region. Glx and tCho in relation to tCr were calculated in the same way.

For the assessment of asymmetries in the metabolism of tNAA, Glx and tCho respectively, we used an asymmetry index (AI):

\[ AI = 2(\frac{|R_L - R_R|}{R_L + R_R}) \]

The physicist performing the analyses did not know whether the children were patients or controls.

The MRI examinations of RE children presented in Study I were re-evaluated blinded by the author and R. Raininko simultaneously with additional MRI examinations of RE and controls in this study, and consensus after evaluating each examination was achieved.

Study III

A neuropsychological test battery mostly consisting of well-known neuropsychological tests of memory and executive functions was administered. The test battery was administered and evaluated according to a manual from the Department of Psychology at the University of Melbourne (135) translated and adapted for use in Sweden by Croona, Hulterström and Kihlgren and validated for Swedish school children (136). The tests evaluate information processing, executive functions and immediate and short-term memory.
The following neuropsychological tests are included in the battery:

**Visuo-spatial skills**
- Block Span Test (137)
- Complex Figure of Rey * (138)
- Spatial Learning test * (139)

**Auditory-verbal skills**
- Digits Forward (140)
- Rey Auditory-Verbal Learning test * (RAVLT) (141)
- Story Recall A+B* (142)

**Executive functions**
- Tower of London (143)
- Verbal Fluency (144)
- Trailmaking A & B (145)

The tests indicated with * comprise subtests of memory; new learning and recall of new learning after 30 minutes.

Intellectual ability was measured by Ravens Coloured Progressive Matrices (146). Neurobehavioral questionnaires were administered to the children’s parents and their teachers. The questionnaire consisted of statements regarding attentiveness, hyperactivity, impulsivity, emotional control, aggressive behavior and so on. It was evaluated on 70 Swedish school children (136) and considered as a valid tool.

**Study IV**
A set of tests was chosen measuring oral, lingual and facial movements, sensibility of lips and tongue and of word retrieving. Additionally, tests of reading techniques and dichotic listening were performed.

Three experienced speech- and language therapists performed the assessments in the afternoon after school for the day, and most often pair wise, i.e. a patient together with his/her control. The procedure took less than one hour per child. Selected parts of the examinations were video or audio recorded. General observations concerning concentration, pragmatic competence and tonus were performed, and deviations in the anatomy of the oral cavity, face, head and neck were registered by visual examination.

The quality of the motor performance was evaluated by scoring from 0 to 3 (no problems 0, slight 1, moderate 2 and severe 3).
Oral and facial motor assessments
- Lip and tongue movement (quality).
- Facial expressions (quality).
- Repeated consonant-vowel (CV) syllables (quality and speed).
- Articulation of a series of nonsense words and tongue-twisting words (quality and speed).

Sensibility tests
- Two-point discrimination (10, 5 and 3 mm distance, respectively) was tested on the lips and at the tip of the tongue. Each distance was tested ten times consecutively and the percentage of correct judgment was calculated.

Oral and written language tests
- Rapid Confrontation Naming test: 80 pictures of ordinary items are presented to the child who is requested to name these correctly as quickly as possible (147).
- Orthographic decoding test*: the child was asked to choose words that appeared real and were correctly spelled (148).
- Phonologic decoding test*: the child should choose words sounding as real words (148).

Each test was time-limited to two minutes, and the results transformed into stanine-scores.

The child’s own estimation of its reading comprehension was documented.

Dichotic listening test *
The test was performed according to the routine practiced at the Department of Speech and Language Therapy at the University Hospital, Uppsala. Pairs of different nonsense CV syllables were presented in both ears simultaneously by a headset from a computerized program (CADDIC DC 1-324 VC, Consonant Int. Ltd, Uppsala, Sweden) in a soundproof studio. The syllables were combinations of six consonants /p/, /t/, /k/, /b/, /d/, and /g/, with the vowels /i/, /a/ or /u/.

The test was administered in a non-forced condition, i.e. no specific attention instruction was given. The child was asked to repeat both CV syllables immediately without being requested to lateralize, and the number of correct syllables for each ear and of correct pairs were registered. During fifteen minutes the child was exposed to 108 pairs of CV syllables.

The tests indicated with * were later added to the study and therefore performed on a subgroup consisting of 13 children with RE and 14 controls.
Statistics

A Mann-Whitney U test was used for analyzing continuous non-parametric variables or small samples, and independent t test with Bonferroni correction for comparing normally distributed continuous variables. Pearson’s two-tailed correlation coefficient was applied for calculating agreements between parameters. A p value of <0.05 was considered statistically significant.

The SPSS 10.0 software package (SPSS Inc. Chicago, IL) was used for calculations.
Results

Study I

Using visual evaluation MRI showed an obvious hippocampal volume asymmetry in five children (28%); in three the left hippocampus was smaller than the right and in two the right was smaller than the left (Fig 4). High signal intensities on T2-weighted images were detected in two of the smaller hippocampi, focal in one and diffuse in the other (Fig 5). Additionally, in one child without hippocampal asymmetry a high signal focus was detected in the right hippocampus. In all six cases, the affected hippocampus was ipsilateral to the side of the RD predominance.

Five children (28%) showed focal high signal intensities on T2-weighted images subcortically in the frontal and temporal lobes bilaterally (Fig 6). One of these cases also showed a hippocampal asymmetry (case 14). Other abnormalities found were a heterotopic nodule above the right frontal horn with a thin extension towards the convexity (case 2), and an asymptomatic Arnold Chiari type I malformation (case 3). In both cases a hippocampal asymmetry was evident.

A follow-up MRI examination was performed after one to three years in six children with abnormalities and these findings remained unchanged. The results of the neuroimaging Study I is presented in Table 3.

Summary: MRI in children with RE revealed some abnormalities in 10/18 (56%) of the children. Thus, eight (44%) MRIs were normal. Hippocampal volume asymmetry and/or high signal intensities in T2-weighted images in hippocampus are demonstrated. MRI also shows high signal intensities in T2-weighted images in the junction between grey and white matter in temporal and frontal lobes bilaterally, irrespectively of hippocampal abnormalities.
Figure 4. Reduced size of the right hippocampus (arrow) (case 1; T1-weighted inversion recovery image).
Table 3. The results of MRI and 1H-MRS (Study I and II, respectively) and EEG. Study I includes cases 1-18.

<table>
<thead>
<tr>
<th>Case /sex</th>
<th>Age at seizure onset (years)</th>
<th>EEG RD lateralization</th>
<th>MRI HC A smallest</th>
<th>Other findings</th>
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<td>4</td>
<td>R</td>
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F: female; M: male; RE: rolandic epilepsy; RD: rolandic discharges; R: right; L: left; NA: no asymmetry; HC: hippocampus; HC A: hippocampal asymmetry; HCR: hippocampal region; HS: high signal and; HSF: high signal focus in hippocampus (T2-weighted images); SHSI: subcortical high signal intensity (T2-weighted images); Het.: nodular heterotopia; AC I: Arnold Chiari I malformation; excl.: 1H-MRS performed but excluded due to suboptimal spectral quality; tNAA: total N-acetyl aspartate; tCr: total creatine; Glx: glutamine/glutamate; AI: asymmetry index. The AIs > 95th percentile of those in controls are indicated in bold.

The ages of cases 19-22 in italics refers to the age of the child when MRI was performed included in study II.
Table 3. Continued.

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<th>Case No. in Study II</th>
<th>MRI</th>
<th>Glx/tCr</th>
<th>tNAA/tCr</th>
<th>HC A</th>
<th>Age (years)</th>
<th>Study II</th>
<th>L HCR</th>
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41
Figure 5. Diffuse increased signal intensity of the left hippocampus (arrow), which is brighter than the adjacent cortex, whereas the normal right hippocampus and the adjacent cortex show the same signal intensity (case 2; T2-weighted spin echo image).

Figure 6. High signal intensities in the superior frontal gyrus in three consecutive 2.5mm thick slices (case 7; T2-weighted spin echo image).
Study II

$^1$H-MRS (Table 3 and 4)

$^1$H-MRS examinations with high spectral quality of the HC region bilaterally were obtained in 13 RE children and 15 controls. AIs were not age dependent in neither children with RE nor in controls. Thus, they are handled as one entity in the statistical calculations.

The AI of the tNAA/tCr ratios was significantly higher in the patients than in the controls ($z=4.49; p<0.001$). In seven patients, the tNAA/tCr ratio was lower in the left, and in six in the right hippocampal region. The AI of the Glx/tCr ratios in the patients was not significantly different compared to controls ($z=1.54; p=0.123$). In five patients the AIs of Glx/tCr were above the 95th percentile of those of the controls. There was no significant correlation between the lateralization of the tNAA/tCr and Glx/tCr ratios. The AI of tCho/tCr ratios was similar in both groups.

Representative spectra of a normal and an abnormal hippocampal region are shown in Fig. 7 and results presented as box plot diagrams in Fig 8 and 9.

Figure 7. LCMModel analysis of a $^1$H-MRS spectra of case 19. The dotted curves display the spectra as measured. The solid curves show the fitted spectra. LCMModel spline baseline was subtracted from all spectra. The left hippocampal region (a) shows a normal spectrum (tNAA/tCr, 2.06) and the right (b) an abnormal spectrum (tNAA/tCr, 1.40).

NAA, N-acetyl aspartate, Cr, creatine, Cho, choline; Ins, myo-inositol; ppm, parts per million.
Figure 8. Boxplots showing the asymmetry index of tNAA/tCr in the hippocampal region in RE children and controls. The ends of the boxes fall at the upper and lower quartiles, the solid line in the middle of the boxes is the median; and the whiskers represent the range of the data.

Figure 9. Boxplots showing the asymmetry index of Glx/tCr in the hippocampal region in RE children and controls. The ends of the boxes fall at the upper and lower quartiles, the solid line in the middle of the boxes is the median; and the whiskers represent the range of the data.
Table 4. The result of $^1$H-MRS of hippocampal region in RE children and controls.

<table>
<thead>
<tr>
<th>Metabolite ratio</th>
<th>Left</th>
<th>Right</th>
<th>Asymmetry Index</th>
</tr>
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<tr>
<td><strong>tNAA/tCr</strong></td>
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<tr>
<td>RE, median (range)</td>
<td>1.57 (1.25-2.06)</td>
<td>1.50 (1.18-2.43)</td>
<td>0.22 (0.11-0.46)</td>
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<tr>
<td>Controls, median (range)</td>
<td>1.43 (1.16-1.76)</td>
<td>1.44 (1.22-1.78)</td>
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<td>95th percentile of controls</td>
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<td>0.086</td>
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<tr>
<td>p value RE vs. controls</td>
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<td>&lt;0.001</td>
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<td><strong>Glx/tCr</strong></td>
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<td>RE, median (range)</td>
<td>1.64 (1.24-2.92)</td>
<td>1.58 (0.70-4.33)</td>
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<td>RE, median (range)</td>
<td>0.28 (0.19-0.33)</td>
<td>0.29 (0.16-0.39)</td>
<td>0.098 (0.011-0.58)</td>
</tr>
<tr>
<td>Controls, median</td>
<td>0.25</td>
<td>0.35</td>
<td>0.097</td>
</tr>
</tbody>
</table>

tNAA: total N-acetyl aspartate; tCr: total creatine; Glx: glutamine/glutamate; tCho: choline compound.

**MRI (Table 3)**

Four of 13 MRIs in the RE group showed a distinct asymmetry, and in all cases the left hippocampus was smaller than right. In one case (case 18) the result deviated from Study I. In the first study it was evaluated as normal, while in this study the left hippocampus was evaluated smaller. The lateralization of a smaller hippocampus corresponds with lateralization of the lower tNAA/tCr ratio in three of four cases.

In the control group, a subtle hippocampal asymmetry were revealed in four of 13 MRI examinations, in all cases left being smaller than right. These findings can be attributed to normal variation of left being smaller than right.

**Summary:** $^1$H-MRS of hippocampal region in children with RE demonstrates an asymmetry of neuronal function evaluated by tNAA/tCr ratio compared to matched controls. MRI reveals hippocampal volume asymmetries in both patients and in matched controls, though more distinct in the epilepsy group. The sample size is too small for estimating correlations regarding volume and metabolic results.
Study III

Results presented as mean and standard deviations (SD) of the neuropsychological tests are presented in Table 5.

Table 5. Mean (SD) neuropsychological test results for children with RE and matched controls.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
<th>RE</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate memory/speed of processing</td>
<td>Block Span</td>
<td>4.4 (0.9)</td>
<td>5.2 (0.8)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Digit Span</td>
<td>3.7 (1.4)</td>
<td>4.6 (1.5)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Trail Making A</td>
<td>5.5 (2.6)</td>
<td>6.8 (2.0)</td>
<td>ns</td>
</tr>
<tr>
<td>New learning</td>
<td>Spatial learning test, recall</td>
<td>7.6 (2.6)</td>
<td>8.6 (0.8)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>RAVLT, five trials</td>
<td>3.4 (1.3)</td>
<td>6.1 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>RAVLT, recall</td>
<td>3.6 (2.0)</td>
<td>5.8 (1.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Story recall A+B</td>
<td>5.7 (2.3)</td>
<td>8.0 (1.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Complex Figure of Rey, recall</td>
<td>3.6 (1.8)</td>
<td>4.9 (1.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Recall of new learning after 30 min</td>
<td>RAVLT, delayed recall</td>
<td>3.4 (1.9)</td>
<td>5.9 (2.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Story recall II</td>
<td>5.1 (2.5)</td>
<td>7.8 (2.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Spatial learning test II</td>
<td>6.7 (2.9)</td>
<td>7.5 (1.9)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Complex Figure of Rey II</td>
<td>4.1 (2.2)</td>
<td>4.6 (2.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Executive functions</td>
<td>Verbal fluency FAS</td>
<td>3.4 (1.6)</td>
<td>5.6 (1.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Trail making B</td>
<td>5.0 (2.0)</td>
<td>6.5 (0.8)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Complex Figure of Rey, organization</td>
<td>4.7 (2.4)</td>
<td>5.4 (2.0)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Tower of London</td>
<td>5.0 (2.1)</td>
<td>6.8 (1.6)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

RAVLT: Rey Auditory-Verbal Learning test; FAS: initial letters for generating words; ns: non significant (t-test).

Intellectual measurement (IQ)
RE group 96.8 (65-115) and control group 95.3 (75.110), i.e. no difference.

Neurobehavioral variables (questionnaire)
Parents evaluation: greater difficulties in RE group compared to controls regarding distractibility (t[32]=2.04, p<0.05), concentration (t[32]=3.20, p<0.01), temper (t[32]=3.98, p<0.001), impulsiveness (t[32]=2.08, p<0.05) and ability to understand instructions (t[32]=2.06, p<0.05).
Teacher’s evaluation: no differences were seen between the groups.
**Academic achievement**

According to the teacher’s evaluation, the RE group had difficulties in reading comprehension compared with controls ($t[32]=2.16$, $p<0.05$).

**Summary:** Neuropsychological assessments disclose auditory-verbal and executive dysfunctions in children with RE compared to matched controls. Visuo-spatial tests did not show differences between the groups. The RE children had more behavioral problems compared to controls according to questionnaires answered by their parents. The non-verbal IQ was normal in both groups.
Study IV

The results of oromotor and sensibility tests are presented in Table 6.

Table 6. Results of oromotor and facial performance, sensibility and language tests in children with rolandic epilepsy and controls.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Method</th>
<th>No. examined</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial movements</td>
<td>Facial expression (forehead, nose, eyes)</td>
<td>20 / 24</td>
<td>ns</td>
</tr>
<tr>
<td>Oral movements</td>
<td>a) Lip movements, quality 20 / 24</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) Tongue movements, quality 20 / 24</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c) CV syllable, quality 20 / 24</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total score (a-c) 20 / 24</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CV syllable, speed 20 / 24</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Articulation</td>
<td>Nonsense words, quality 13 / 14</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tongue-twisting words, quality speed 13 / 14</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Sensibility</td>
<td>Two-point discrimination 20 / 24</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td>Rapid Confrontation Naming (149)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Speed and quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reading technique tests (148)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Orthographic decoding 13 / 14</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phonologic decoding 13 / 14</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reading comprehension 13 / 14</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

ns: not significant (Mann Whitney U test).
Dichotic listening test (Table 7)

In the RE group all children showed a right ear advantage (REA). In the control group twelve children showed REA, the two left-handed children included, and two had a left ear advantage. There was a significantly lower performance of correct CV syllables in the RE group compared with controls.

Table 7. Results of dichotic listening test in 13 children with rolandic epilepsy (RE) and 14 controls.

<table>
<thead>
<tr>
<th></th>
<th>RE (%)</th>
<th>Controls (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct right ear</td>
<td>60.6</td>
<td>68.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Correct left ear</td>
<td>40.8</td>
<td>56.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Correct right + left</td>
<td>15.9</td>
<td>33.4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Mann-Whitney U Test was used.

Significant correlation was found in the RE group between correct right ear performance and a lower score of tongue movements ($r=-0.65; p<0.05$) as well as to the total score of oromotor score (lip and tongue movements and CV syllable quality) ($r=-0.57; p<0.05$). These correlations were not found in the control group. Performance on phonological reading test showed a positive correlation to correct left ear performance in the controls ($r=0.75; p<0.01$), which was not found in the RE group. There was no correlation concerning a better DLT performance and age or duration of epilepsy in the RE group, or of age in the control group.

Summary: Children with RE show oromotor dysfunctions compared to controls concerning tongue movements, repeated CV syllables and articulation of tongue-twisting and nonsense words. They also show a poorer performance in dichotic listening than matched controls.
The delineation of ‘classical’ RE and related conditions in the literature is sometimes imprecise and confusing. A simple classification is proposed until genetic studies may clarify the issue:

1. RE ‘pure’ according to the original definition.
2. RE ‘plus’ including entities as benign partial epilepsy with affective symptoms and autosomal dominant rolandic epilepsy with speech dyspraxia. Also RE with some abnormal EEG patterns can be included here.
3. RE-related disorders as ABPE, epilepsy with CSWS and LKS.
4. Structural brain lesions with signs and symptoms as in RE.
Discussion

Classification and diagnosis of RE, inclusion and exclusion criteria (Study V)

There is a never ending discussion among epileptologists about classification of seizures and epileptic syndromes. This is perhaps more obvious among neuropediatricians because of the dynamics of childhood epilepsies and the fast developing genetic knowledge about epileptic syndromes over the last decade. There is a general agreement that it is essential to have uniform criteria for each epileptic syndrome in order to communicate the different clinical aspects of these syndromes. Ever since the latest proposal for classification of epilepsies and epileptic syndromes by the Commission on Classification and Terminology of ILAE in 1989 (2), a discussion concerning classification has taken place, but so far there has not been any consensus for a new one.

Awaiting this, the ILAE Task Force on Classification and Terminology in 2001 suggested a proposed diagnostic scheme for people with epileptic seizures and with epilepsy (150). This scheme consists of five ‘axes’: 1) ictal phenomenology, 2) seizure type, 3) syndrome, 4) etiology and 5) impairment. The scheme is intended to provide the basis for a standardized description of individual patients rather than a fixed classification, and the development of a specific classification should be regarded as a continuing progressive work. Some changes of vocabulary are proposed, e.g. ‘focal’ replaces both ‘partial’ and ‘localization-related’ and ‘febrile seizures’ should be used instead of ‘febrile convulsions’. Consequently, RE in this description is an example of an idiopathic focal epilepsy and remains denominated as ‘benign childhood epilepsy with centrotemporal spikes’. In the third axis ‘benign epilepsy syndrome’ is defined as ‘a syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae’. In RE, there are sometimes seizures that are intractable or difficult to treat for a period, including some of our cases (see below). However, in general and in the long run the RS can be considered as easy to treat.

The first axis, ‘ictal phenomenology’, is probably useful in describing or defining RS and in the second axis, ‘seizure type’, the focal elementary clonic motor signs and focal elementary sensory symptoms should be the appropriate seizure components of RS including sialorrhea.
It is important to have representative children included in studies of particular epileptic syndromes and avoiding selection bias has to be emphasized.

The delineation of RE is discussed in Study V where the typical electro-clinical syndrome of RE according to the ILAE definition of 1989 (2) is proposed to be called RE ‘pure’ in order to stress the boundary to other conditions with RD, which often have been confused with RE. As a consequence of this, reliable comparisons of study results are doubtful. An example is the neuropsychological study of Weglage et al. (94) on a group of children with RD but including individuals both with and without RS, which were considered as one group. Moreover, some studies of ‘atypical RE’ should have been assigned to conditions other than RE ‘pure’ (32, 57). Wirell et al. (32), after having done a retrospective evaluation of 42 children diagnosed as RE, suggested that the occurrence of atypical electro-clinical features is the rule rather than the exception. By classifying clinical features like Todd’s paresis, diurnal-only seizures, concomitant attention deficit disorder and SE as atypical, they found that 50% were clinically atypical. However, this is a too narrow delineation of RE according to many authors (18, 31), an opinion to which I agree. Furthermore, of most importance is that the ILAE definition of RE and of idiopathic epilepsies do not expressly reject these features. In our material one boy with postictal Todd’s paresis was included. Concerning EEG, Wirell et al. (32) found atypical features as abnormal background activity and atypical spike morphology in 31%, which definitely disqualifies the RE diagnosis according to the ILAE definition.

In cases with obvious brain lesions (e.g. widespread cortical malformations, porencephalic cysts, post infectious and traumatic lesions, tumors (58-61, 65, 66, 151)) and concomitant RD, one must be very cautious to classify these into RE (our RE ‘pure’) even if the seizure semiology and seizure outcome happen to be in accordance. The reported studies are interesting as they demonstrate the variability of phenotypes in focal idiopathic epilepsy but are proposed to be separated from RE ‘pure’ into the group ‘structural brain lesions with signs and symptoms as in RE’. On the other hand, when lesions are distant from the rolandic area, they may be included as RE ‘pure’.

In Study I we presented one girl with Arnold Chiari malformation type I and another girl with an isolated heterotopia above the frontal horn contralateral to the RD. In neither of these cases, there was a relation between the electro-clinical symptomatology and the abnormalities. However, children with cerebral palsy have been included in previous studies (17, 21). It has to be admitted, that the distinction between what should be regarded as casual findings, and findings which may have an impact on the epileptogenesis, is a difficult issue in some cases.
Is it justified to classify an individual as having RE after only one seizure provided that both EEG and semiology are those of typical RE? Some investigators agree to this (11, 18), but this is against the established definition of epilepsy. In the present studies we demanded two or more seizures as mandatory for inclusion. In several cases, the first few seizures were presented as nocturnal GTCS without preceding observation of focal signs, which is a common course in RE. Appropriate age, normal neurologic examination, no history of brain lesions and awake and/or sleep EEGs showing RD, qualifies for the RE diagnosis.

Repeated normal EEG examinations with sleep recordings are very rare and the diagnosis of RE in such patients should be accepted only with great reservation (127). In order to follow the RE criteria strictly, a girl with several typical RS was excluded from Study IV after initial inclusion due to absence of RD in three consecutive EEG recordings including sleep.

Two pairs of siblings were included in the study group, two in Study I and III and one of these also in Study II. The families of those children were also included in a genetic multicenter study, which provided evidence for linkage of the electrographic pattern (RD) to chromosome 15q14 (109). However, the genetics of RE is still to be clarified, and when this is achieved, it will bring about an improved diagnosis of RE and related conditions.

It may be indicated to perform EEG on siblings and controls if an investigation mainly concerns EEG studies. However, one must bear in mind that population studies have shown an RD incidence of approximately 3% in children aged 3–14 years (40) which can confuse the results.

The localization of RD in our subjects is mainly in the rolandic and peri-rolandic area, i.e. corresponding to the centrottemporal or midtemporal, but also parieto-occipital and fronto-temporal leads in EEG in accordance with RE (45, 152). The discharges seem to ‘migrate’ in a posterior- anterior direction with increasing age. Drury and Beydoun (45) stated that posterior or occipital RD may be related to RE as well and most important is the monomorphic sharp wave and not the location. This has also been confirmed in studies using magnetic encephalography (MEG) (153, 154).

The course and prognosis of all included subjects in this study is in accordance with RE. A few children, including the index case, have had frequent and medically resistant seizures periodically for some days or a few weeks until the change of treatment had been accomplished. None had SE, nor signs of oromotor difficulties interictally. Three children (8%) have had recurring sporadic RS for more than 3 years, where such recurrences can occur in 7% of children with RE (11).
Magnetic resonance imaging (Study I)

In Study I a series of children with typical RE, examined by MRI, was presented and by visual evaluation a hippocampal volume asymmetry was found in five cases.

Few MRI studies have been performed on children with RE using modern techniques. Kohrogi et al. (155) (in Japanese) reported hippocampal volumetric measurements in 27 patients with BCECT, age 6–19 years, in 22 patients with TLE, age 5–22 years, and in 17 normal control subjects, age 6–15 years. The hippocampal volumes and the right minus left-side volumes were not significantly different in the three groups, but the values in the TLE group were more scattered. Moreover, there was no abnormal signal intensity in the hippocampus and no specific abnormality in the surrounding structures. Thus, these normal results in the children with RE deviate from our study and also from other reports of normative data, which will be discussed in the following. However, the normal findings, even in the TLE group, raise doubts as to whether a comparison can be made because of the different techniques.

Gelisse et al. (61) retrospectively evaluated 98 consecutively referred children with RE during a 15-year period in which 28 had undergone MRI. Five of the examinations revealed pathology consisting of a slight ventricle dilatation and ‘hypersignals’ in white matter, moderate enlargement of the right temporal horn, cavum septum pellucidum, bi-opercular polymicrogyria, and marked right hippocampal atrophy, respectively. The latter findings was reported separately (64), and the authors concluded that there was no causal connection between the RE and this finding. To our knowledge there are no prospective or longitudinal MRI studies in RE.

Is volumetry of the hippocampus a more reliable method than visual evaluation? Are the asymmetries found beyond the normal variation in children, and are our results reproducible?

Volumetry has the advantage of being objective and sensitive. The method provides quantitative data and detects bilateral atrophy. However, the method requires normative data and high intra-rater reliability. Further, it is labor-intensive and time-consuming. Volumetry can improve detection of hippocampal volume loss but only by 5-8% over visual evaluation (Kuzniecky, personal communication). In order to compare the diagnostic accuracy between visual assessment and volumetry, Cheon et al. (156) studied 48 adults who underwent surgery for TLE and found that visual assessment was slightly superior in estimating unilateral hippocampal sclerosis. Berkovic et al. (157) came to the same conclusion, whereas other authors present an opposite opinion (158, 159).

There is some normative data reported in children. Giedd et al. (160), investigating 99 normal children age 4–18 years reported a ‘right-greater-than-
left’ asymmetry of the hippocampus with no proportion given. No age dependency was seen. Ho et al. (161) examining eight normal children age 3–15 years, found that the left hippocampus was 8% smaller than right. Utsunomiya et al. (162) performed MRI in 42 children aged 3 weeks–14 years with other neurological findings. Volumetry of hippocampal formation showed a larger right than left side in 91%. In the older age group a difference of approximately 8-10% was found. This was not seen in the youngest children. In adults, there are numerous reports of the left hippocampus being smaller than the right in healthy individuals, but also absence of side-to-side asymmetry (163).

The asymmetries found in Study I in the three ‘left-smaller-than right’ cases by visual assessment are obviously outside of the normal range. The two ‘right-smaller-then-left’ cases are definitely abnormal. The high signal lesions seen in the hippocampus in three children were slight and we do not consider these findings as signs of mesial temporal sclerosis.

The high signal intensities on T2-weighted images in the junction of white and grey matter observed in five children were located in the temporal poles and in the frontal lobes. This can be interpreted as a possible expression of delayed maturation. Similar findings have not been described earlier in other idiopathic epilepsies. MRI performed on six children about three years after the first examination showed these abnormalities to be stable. This may be due to too short intervals between the examinations and the young age of these children. As the high signal lesions were permanent, we could also exclude the possibility that they were a result of recent seizures which have been reported to cause this kind of lesions in grey matter (164, 165). The clinical significance of these findings remains unclear, but a longer follow-up period will probably clarify the issue.

The other abnormal MRI findings, a heterotopia (case 2, Table 3) and an Arnold Chiari type I malformation (case 3, Table 3), are considered as coincidental. An Arnold Chiari type I malformation has been described in one child with RE in a report by Kramer et al. (63). Few cases of cortical malformations in RE have been reported, some incidental (61, 65), and one considered as causing RD and RS (66). Cendes at al. (166) stated that neuronal migration disorders, including nodular heterotopia, are more likely associated with hippocampal atrophy (‘dual pathology’), independent of the distance of the lesion from the hippocampus. We consider our case 2 with a heterotopia above the right frontal horn, similar to focal transmantle dysplasia and a smaller hippocampus contralaterally as coincidental.

A limitation of Study I is the lack of control subjects. The observer of the MRIs was aware of the epilepsy diagnosis, but not of the electrographic fea-
tures. In Study II, we blindly re-evaluated the MRIs included in Study I as well as additional MRIs. We consider the blinded evaluation in connection with Study II as the most appropriate and reliable one.

\(^{1}\)H-MRS (Study II)

Is the asymmetry of tNAA/tCr ratios in the hippocampal region in RE children demonstrated in Study II valid and of any clinical significance?

Few reports on normative data of \(^{1}\)H-MRS in children are available. Choi et al. (86) examined 17 healthy children age 3–14 years and found symmetric ratios of NAA/tCr in the allocortex which comprises the hippocampus and a part of the parahippocampal gyrus included in a 5 ml voxel. In our study, however, we found asymmetries. The difference may depend on the fact that Choi et al. compared the mean ratios of each side, while in Study II AI was calculated in the patients and compared with controls (median AI 0.22 in RE, 0.045 in controls). In our study, the median of the tNAA/tCr ratios of the hippocampal region was principally the same (see Table 4). Compared to Choi et al. we used a considerably larger voxel size (16 ml), apparently covering more than solely the hippocampus (the volume estimated to approximately 3-5 ml by volumetry in adults), i.e. part of the parahippocampal gyrus and cerebrospinal fluid (CSF) are included. Thus, we called the investigated volume the ‘hippocampal region’. This may influence the spectral profile, however, by using ratios of the metabolites and calculating AI, the influence of CSF on the results can be regarded as minimal. An advantage of the large voxel size is a better signal-to-noise ratio.

Evidently, \(^{1}\)H-MRS most appropriately reflects the neuronal function of the hippocampus or hippocampal region, whereas MRI studies the morphology. \(^{1}\)H-MRS has especially been useful for lateralizing the epileptogenic zone in MRI negative TLE (67, 167). NAA is confined to neurons and neuronal processes both in grey and white matter and a decreased concentration indicates loss of neurons or a neuronal dysfunction (168, 169). Kuzniecky et al. (170), in a study including MRI volumetry, \(^{1}\)H-MRS and histopathology in adults with TLE, found that the neuronal-glial ratio in the resected hippocampus correlated with hippocampal volumetry but did not correlate with the metabolic measurement obtained with \(^{1}\)H-MRS. The conclusion was that the metabolic events measured by \(^{1}\)H-MRS reflect neuronal and glial dysfunction rather than neuronal cell loss.

As NAA can be regarded a marker of neuronal function, it is evident that \(^{1}\)H-MRS has the potential for being a tool in cognitive assessment. A number of studies in epilepsy populations have begun to elucidate this field of research. In a study of 22 children with intractable TLE, Gadian et al. (171) found that verbal IQ correlated selectively and significantly with left mesial temporal NAA/Cr+Cho ratios, whereas nonverbal IQ correlated selectively
and significantly with right mesial NAA/Cr+Cho. In an adult population with TLE Martin et al. (172) found a significant negative correlation between Cr/NAA ratios of the left hippocampus and verbal memory. A few other authors have examined various cognitive functions with hippocampal 1H-MRS (173, 174) and this area of work is under development.

The rationale in performing the 1H-MRS study of the hippocampi was firstly the asymmetrical hippocampal findings of the MRI study, and secondly, which is more important, the results of the neuropsychological Study III showing cognitive deficits in RE children. Other groups have reported similar results, which will be reviewed in the following. However, our sample of only eight of the RE children participating in both studies, is too small for making any reliable correlations between the results of Study II and III.

Is it possible that AED treatment can influence the 1H-MRS results? All our six children on medication were prescribed fairly moderate dosages and no one showed signs of adverse effects. We consider such an influence as unlikely, but there are few studies concerning this subject. Simister et al. (72) in a 1H-MRS study of the frontal lobes (both grey and white matter) in 21 adults with idiopathic generalized epilepsy, showed a lower myo-inositol in a subgroup taking valproate but otherwise no interaction with AED was noted. Compared with controls, an elevation of Glx and a reduction of NAA were observed.

Concerning Glx, glutamate is the chief excitatory neurotransmitter, thus an indicator of hyperexcitability in the epileptogenic zone. In our study, there was a tendency towards a higher AI of the Glx/tCr ratio in the RE group compared to the controls, which may reflect an imbalance in the hippocampal region of this neurotransmitter. However, a higher resolution of the spectra and a larger sample is needed to achieve more reliable results.

Neuropsychological assessment (Study III)

The most evident findings in the neuropsychological study were deficits in the performance of auditory-verbal memory and learning assessments in the RE group compared to their matched controls. The RE children disclosed problems concerning their capacity for both new learning and long-term recall according to RAVLT and Story Recall tests. Metz-Lutz et al. (175) found a significantly lower result of RAVLT in RE children with right-sided RD. They also investigated the children within two weeks from the first seizure and a significant cognitive weakness mainly in subtests involving short-time memory learning and attention was disclosed. The shortcoming in the auditory-verbal domain has also been pointed out in other similar studies of RE children (95, 96). The only subtest of auditory-verbal function measurement, which did not show any group difference, was the Digit Span test reflecting immediate memory function.
Test results showing the children’s executive abilities were significantly poorer compared with controls. This has also been shown regarding Word Fluency by Baglietto et al. (96).

The subtests of the visuospatial domain failed to detect any differences between the groups. This result conflicts with the findings of other authors (91, 93, 96, 176), but few studies on visuospatial functions are performed in RE.

The outcome of the neurobehavioral variables evaluated by questionnaires, contradicts previous studies (89), but confirms some of the findings in more recent studies (93, 97, 175, 177, 178). A problem of selection bias in previous studies has been the exclusion of children with ‘neuropsychiatric abnormalities’ (11). The close relation between RE and individuals with just RD and neurobehavioral disorders has been pointed out by Doose (179). Holtmann et al. (180) found RD without seizures in 5.6% of 483 children diagnosed with ADHD, which is significantly higher than found in normal children (27, 40). The association between two common childhood disorders might be coincidental, or an expression of a common hereditary impairment of brain maturation (108). In our study, it cannot be excluded that the neurobehavioral problems in the RE children maybe a confounding factor for the results of the executive tests.

Concerning intelligence measurements by Raven’s coloured matrices, no difference was seen between RE children and controls. This is in accordance with most other studies. Beaussart (10) studied 221 children with RE and found a normal prevalence of slight mental retardation, however, Beaumoiron et al. (49) found two of 26 children with RE who had low IQ scores.

It is now well established that a proportion of children with RE has some degree of cognitive dysfunction. A follow-up study after approximately three years of the children included in Study III and an additional 16 children with RE has been performed by Lindgren et al. (personal communication). These results show normalization of all variables compared to control children, even though the RE children still scored lower in the Verbal Fluency test than the controls.

Oromotor assessments (Study IV)

In Study IV the oromotor assessments disclosed differences in tongue mobility and articulation between RE children and controls. Normally, the child with RE has no obvious speech problems, but there have been several case studies reporting more prolonged or repeatedly occurring oromotor dysfunction combined with speech defects. This has been reported in patients having partial SE (34, 35, 37, 38, 98), and in connection with the initial phase of the epilepsy with marked epileptiform activity in the EEG (36, 87, 99-101, 181), a phase which has also been entitled ‘acute’ (100).
There are few reports concerning oromotor assessments of RE children in an ‘active’, but not ‘acute’ phase similar to the children participating in Study IV. Staden et al. (95) revealed abnormalities in dyspraxia screening in nine children, most frequently concerning lip and tongue movements and difficulties in articulating a sequence of syllables. However, they rarely found problems with articulation of ‘complex words’, which are similar to tongue twisting words used in our tests, and caused marked problems in the RE group in Study IV.

The brief assessments concerning language function included in Study IV did not reveal any differences between the RE and control children, which is in agreement with other reports (38, 95). Staden et al. (95) found some degree of language dysfunction in 13 out of 20 children with RE concerning reading, spelling and expressive grammar. There may be a selection bias, however, in that the parents of 11 of 20 children were concerned about their children’s language and learning problems. An additional report of RE has found some degree of language dysfunction or delay in RE children (97).

Dichotic listening (Study IV)

Dichotic listening test showed a significant poorer result in the children with RE compared with controls. Normative data for our age group and for the method used in the present study are lacking. Hugdahl (personal communication) reported data from ‘The Bergen dichotic listening database’ with slightly different methods concerning children age 8-15 years. These data show around 45% correct for the right ear and around 42% correct for the left ear. According to these figures, the children with RE in Study IV performed almost normal, contradicting our results which were compared with controls. Dichotic listening has been used in investigating RE children by Metz-Lutz et al. (175) who found an ‘impaired divided attention’ in eight of 22 children with RE, which seems to be similar to our results. Moreover, Hommet et al. (182) used dichotic listening in 23 adolescents and young adults who were ‘in complete remission’ of RE, i.e. no seizure activity or abnormal EEG tracing had been seen ‘for at least one year’. No difference in performance between patients and controls was found, which may be an illustration of maturation of the auditory system in this older age group compared to our children.

The theoretical background to the findings of deviating DLT performance in our RE group may be the proximity of the rolandic and perirolandic areas to Heschl’s gyrus, which mainly consists of Brodmann’s area 41 and 42. This area contains the primary auditory receptive area, which is essential for discriminations requiring a response to changes in the temporal patterning of sounds and for recognition of the location or direction of sounds. Hypothetically, epileptic activity in an adjacent area, i.e. the lower rolandic cortex, may disturb the optimal function of auditory perception.
Figure 10. Lateral view of the left cerebral hemisphere. The positions of the EEG surface electrodes according to the International 10-20 system are indicated.

Figure 11. Coronal section of the right cerebral hemisphere.
Neurophysiology and summary

The ‘rolandic area’ or ‘rolandic cortex’ comprises the gyri on each side of the rolandic fissure or central sulcus, i.e. the pre- and postcentral gyri responsible for the typical semiology of RS (see Fig10). The lower boundary is the upper bank of the sylvian fissure. The upper boundary, however, is not distinct.

In EEG terminology, RD are located ‘centrotemporal’ or ‘midtemporal’, but the semiology of RS is rarely if ever referable to the temporal lobe. The classification of focal (partial, localization-related) seizures as in RE may give the false impression of the existence of an epileptic region comprising a small and well-delineated focus of neuronal pathology. However, focal seizures and focal syndromes are almost always due to diffuse, and at times widespread, areas of cerebral dysfunction (183). It is also a well-known fact that the RD in EEG are quite widespread. Legarda et al. (152) found that RD are exclusively suprasylvian in origin disclosing high central and low central subgroups with different semiology according to the cortical representation. Spike triggered functional MRI (fMRI) (184) performed in a girl with typical RE demonstrated activation of the left facial region of the somatosensory cortex, which was suggested to be consistent with the facial sensorimotor involvement of RS.

MEG studies performed in patients with RE have localized the RD to both the upper and lower rolandic area (153). Moreover, it has been suggested that the RD are generated in the rolandic region near the somatosensory cortex (185, 186) or in the precentral cortex, closer to the second than to the primary somatosensory cortex (154). This may underlie the hyperexcitability of related sensorimotor cortices (187). In this context also maturation in the thalamocortical development process has been mentioned (187).

Studies of RE children including Study III have revealed neurobehavioral problems, which indicates dysfunctions in circuits distant from the rolandic area, i.e. complex circuits in frontal lobes including interhemispheric interactions (175-177). These ‘anatomicofunctional’ circuits mature between childhood and adolescence, i.e. during the same age period as the presence of the active RE. Thus, the course of RE is probably dependent on the maturation of these circuits.

In summary, there are several observations indicating that the neurophysiological background of RE is not only restricted to the rolandic cortex. Indisputably, the intrinsic epileptogenesis is located in this region, but it may be hypothesized that there are other underlying and modifying factors of importance for the syndrome. Our findings of an asymmetric distribution of the marker of neuronal function in the hippocampal region in RE children can be regarded as an additional contribution in this research.
The hippocampus is essential for learning, memory processing and storing and has numerous but mainly indirect connections with the cortex, the so-called neocortical-hippocampal loop, as well as within the limbic system. The hippocampal formation, the entohiral cortex and parahippocampal gyrus (see Fig 11) are all believed to participate actively in the memory processes (188). A hypothesis is that the cognitive deficits demonstrated in RE children are at least partly determined by a maturational dependent defect in these structures and in their neocortical connections.

Limitations of Study I–IV

Overall the sample size in the different studies is small, which is a limitation in statistical calculations. However, non-parametric tests for small samples (Mann Whitney U test) did clearly show differences between RE and control children in Study II and IV, as well as the t-test used for normal distributed material in Study III. The ideal situation had naturally been if the same children participated in all studies, which would have made possible an optimal comparison between the results. It had been even better with longitudinal studies. This age group, 8 to 14 years, is in general co-operative and curious about participating in such investigations. Nevertheless, there are difficulties in recruiting school children in particular for repeated examinations.

The EEG results in the present studies were mainly presented as supporting the RE diagnosis and for showing the lateralization of RD. More thorough investigations were not performed or intended in any of the studies, even if this could have been desired in Study II–IV. Repeated and scheduled EEGs for research purposes are often difficult to obtain because of practical and psychological reasons, e.g. the older children are more sensitive concerning their history of epilepsy.
Conclusions

Investigations of children with typical electro-clinical RE according to the ILAE definition have revealed:

- Hippocampal volume asymmetry by visual evaluation in 5/18 children (28%) and high signal intensities in the hippocampus in 3/18 (17%) where two also showed volume asymmetry. High signal intensities on T2-weighted images in the junction between grey and white matter in temporal and frontal lobes bilaterally in 5/18 children (28%). The clinical significance of these findings is unclear. The last mentioned abnormality may be an expression of delayed cerebral maturation.

- Asymmetry of neuronal function in the hippocampal region assessed by tNAA/tCr ratio in $^1$H-MRS examinations compared with matched controls.

- Dysfunctions in auditory-verbal skills, both regarding new learning and recall of learning and in executive skills compared with matched controls.

- Behavioral problems assessed by parental questionnaires compared with matched controls.

- Oromotor dysfunctions concerning tongue movements, repeated consonant-vowel syllables and articulation of tongue-twisting and nonsense words compared with matched controls.

- Lower performance in dichotic listening compared with matched controls which may indicate slight problems with auditory discrimination.

The results indicate an abnormal neuronal function near or distant from the rolandic and perirolandic area. It is proposed that the cognitive deficits and the oromotor dysfunction demonstrated in children with RE are caused by a defect, or more probably, a delayed myelination in terms of maturation, which may normalize completely or partially. Further studies will clarify this topic.
A classification of RE and related conditions is proposed until results of ongoing genetics research may clarify the delineations:

1) RE ‘pure’, i.e. children included in the studies,
2) RE ‘plus’ (e.g. benign partial epilepsy with affective symptoms and autosomal dominant rolandic epilepsy with speech dyspraxia),
3) RE-related disorders (e.g. atypical benign focal epilepsy, epilepsy with CSWS and LKS)
4) Structural brain lesions with signs and symptoms as in RE.
Future directions

- Follow-up studies of children with RE, both concerning morphology by MRI, and neurometabolism by $^1$H-MRS are important. The spectroscopy technique is improving which increases the possibilities to non-invasively explore the extremely complicated brain. Further neuropsychological studies are also needed, and as mentioned, our team has already performed this (Lindgren et al., personal communication). Electrographic studies in connection with cognitive assessments are also demanded.
- The mentioned studies may explain if maturation of the brain will completely resolve the abnormalities demonstrated in RE children, or if some will remain into adulthood.
- Further genetic studies concerning the idiopathic childhood epilepsies including RE and RD are needed in order to clarify if they may have a common underlying genetic etiology.
- Appropriate delineation of RE and the idiopathic childhood epilepsies are also needed for communication and research. The results of genetic studies will probably be constructive in this topic.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to October, 1985, the series was published under the title “Abstracts of Uppsala Dissertations from the Faculty of Medicine”.)