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Original article

LIS1-associated classic lissencephaly: A retrospective, multicenter survey of the epileptogenic phenotype and response to antiepileptic drugs

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Abstract

Background: Patients with *LIS1*-associated classic lissencephaly typically present with severe psychomotor retardation and drug-resistant epilepsy within the first year.

Aim: To analyze the epileptogenic phenotype and response to antiepileptic therapy in *LIS1*-associated classic lissencephaly.

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Method: Retrospective evaluation of 22 patients (8 months–24 years) with genetically and radiologically confirmed *LIS1*-associated classic lissencephaly in 16 study centers.

Results: All patients in our cohort developed drug-resistant epilepsy. In 82% onset of seizures was noted within the first six months of life, most frequently with infantile spasms. Later in infancy the epileptogentic phenotype became more variable and included different forms of focal seizures as well generalized as tonic–clonic seizures, with generalized tonic–clonic seizures being the predominant type. Lamotrigine and valproate were rated most successful with good or partial response rates in 88–100% of the patients. Both were evaluated significantly better than levetiracetam ($p < 0.05$) and sulthiame ($p < 0.01$) in the neuropediatric assessment and better than levetiracetam, sulthiame ($p < 0.05$) and topiramate ($p < 0.01$) in the family survey. Phenobarbital and vigabatrin achieved good or partial response in 62–83% of the patients.

Conclusion: Our findings suggest that patients with *LIS1*-associated lissencephaly might benefit most from lamotrigine, valproate, vigabatrin or phenobarbital.

Keywords: Lissencephaly; *LIS1*; Epilepsy; Treatment; Brain malformation; Genotype-phenotype relationship

1. Introduction

Classic lissencephaly is a rare brain malformation caused by defective neuronal migration during embryonic development. Birth prevalence is estimated to be approximately 1–4:100,000 newborns [1]. Affected children typically present with severe psychomotor retardation and drug-resistant epilepsy. The seizure disorder commonly manifests in the first months of life with infantile spasms and later includes various seizure types, sometimes progressing to Lennox–Gastaut syndrome [2–4]. Treatment of frequently daily seizures is a major concern for the families and their attending child neurologist. Feeding problems, respiratory infections and status epilepticus are thought to contribute to the high mortality rate of approximately 50% up to the age of 10 years [2,3].

The etiology of classic lissencephaly is heterogeneous and includes Miller–Dieker syndrome as well as isolated monogenic forms. Currently mutations in seven core genes are known to cause classic lissencephaly. In approximately 70% of patients mutations in the *LIS1* (*PAFAH1B1*) gene are detected [5]. While heterozygous deletions or intragenic mutations in *LIS1* lead to the isolated lissencephaly sequence (ILS), variable microdeletions of 17p.13.3 including the *LIS1* gene and additional critical genes (e.g. *YWHAE*) cause Miller–Dieker syndrome [6].

Lissencephaly is radiologically characterized by a smooth and thickened cerebral cortex with reduced or absence of gyration (pachygyria/agyria) instead of the characteristic gyri and sulci of the normal human and primate brain [7].

There is a remarkable genotype phenotype correlation with mutations in the different genes resulting in gene-specific distinct cerebral malformations as seen in magnetic resonance imaging (MRI) as well as gene-specific changes in the unique layering of the cerebral cortex [8,9].

We therefore postulated that the genetic alterations underlying classic lissencephaly not only determine the genotype-specific cortical architecture but may also contribute to the individual epileptogenic phenotype and response to antiepileptic therapy.

To our knowledge, the efficacy of antiepileptic treatment in classic lissencephaly so far was described only in the context of case reports [10–12], in cohorts of patients with intractable epilepsy in general [13] or in animal models for lissencephaly [14,15].

Given the difficulties of performing a prospective randomized study in infants with this rare brain malformation, it was the aim of this retrospective study to systematically describe the epileptogenic phenotype and the response to antiepileptic therapy in a homogenous patient cohort with genetically and radiologically confirmed *LIS1*-associated lissencephaly.

2. Patients and methods

2.1. Patients

Patients were recruited from the genetically assessed lissencephaly cohort in our diagnostic laboratory ($n = 11$) and through the homepage of the patient support group LISS e.V. ($n = 11$). Inclusion criteria for the patients of the present study were: (1) classic lissencephaly (type I lissencephaly) diagnosed by cerebral magnetic resonance imaging (cMRI) and (2) confirmed pathogenic *LIS1* mutation by genetic testing. Available cMRIs of ten patients were re-evaluated by a neuroradiologist (G.S.) and were graded according to Dobyns' lissencephaly patterning scale [16].

The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the ethic committee of the University hospital Regensburg, Germany. A written informed consent was given by all parents as legal guardians.