Focal Epilepsy in Individuals with Laron Syndrome

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\textbf{Keywords} \\
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\textbf{Abstract} \\
\textbf{Objective:} The aim of the study was to describe focal epilepsy in patients with Laron syndrome (LS).
\textbf{Methods:} Data were retrieved from medical records of a single-center cohort of 75 patients with LS.
\textbf{Results:} We describe for the first time 4 patients with concomitant focal epilepsy and LS. Two of them experienced episodes of status epilepticus. Electroencephalogram examination in all 4 patients showed ictal epileptiform discharges in the temporal regions. Three achieved long-term seizure freedom on antiseizure medications.
\textbf{Conclusion:} Patients with LS may be at risk of developing focal epilepsy, which seems to be unrelated to hypoglycemic episodes in childhood.

\textbf{Introduction} \\
Laron syndrome (LS) or primary growth hormone insensitivity (OMIM: 262500) is a rare congenital disease caused by deletions or mutations in the growth hormone-receptor gene with autosomal recessive inheritance. It tends to occur in populations with a high incidence of consanguinity. From infancy, the height deficit ranges from 4 to 10 standard deviations below the median for normal height for age. Patients have a typical appearance that includes a small face, protruding forehead, saddle nose, sparse hair, and obesity, and they have a tendency to hypoglycemia [1].

During 57 years of follow-up of a cohort of 75 LS patients, several neurological manifestations have been described [2]. Untreated patients have a below-normal head circumference, which responds to insulin-like growth factor-1 (IGF-I) replacement treatment [3]. Some patients have abnormal brain structures on brain magnetic resonance imaging (MRI) [4]. Psychological examinations revealed most commonly borderline or below aver-
age intelligence quotient, though intellectual abilities ranged from normal intelligence to severe mental retardation [1, 5].

Hypoglycemia has been described in LS patients, mainly during infancy [6, 7]. Epilepsy as an independent comorbidity of LS has not been reported. We herewith describe, for the first time, the co-occurrence of focal epilepsy as well as status epilepticus (SE) in LS patients, which does not seem to be related to hypoglycemia. We propose that focal epilepsy may represent a previously unrecognized neurological comorbidity of LS.

Methods

Data have been retrieved from medical records of the endocrine and neurology clinics at Beilinson and Schneider Medical Centers. Inclusion criteria were genetically proven LS patients and a diagnosis of epilepsy as determined by a trained neurologist. The study was approved by the local Ethics Review Board.

Patient Descriptions

Principal clinical findings are summarized in Table 1.

Patient #1

This male patient was diagnosed in early childhood with classical LS. He had no documented episodes of hypoglycemia during infancy and was not treated with IGF-1. Around 4 years of age, he had the onset of focal seizures with impaired awareness and a preceding aura that consisted of a weird feeling or fear, dizziness, and blurred vision. Few episodes progressed to bilateral tonic-clonic seizures. Seizures occurred both during wakefulness and sleep and tended to be frequent (initially up to twice daily) and prolonged, lasting up to 10 min. A post-ictal phase characterized by sleepiness or headaches lasted about 1–2 h. Several electroencephalogram (EEG) examinations showed interictal epileptiform discharges (IEDs) in the right temporal head region. He became seizure-free on antiseizure medications (ASMs). He did not suffer from hypoglycemic episodes throughout his childhood or adulthood and had normal glucose levels during his seizures. As an adult, he developed chronic lung disease and passed away at the age of 58 due to pulmonary insufficiency.

Patient #2

This female patient was diagnosed with LS at the age of 2.5 and started IGF-1 treatment at age 3. In subsequent years, her glucose levels were normal, and she had no documented hypoglycemic events during infancy or later in life. She had normal intelligence. Since the age of 6 she had both focal and generalized seizures (the latter probably representing focal to bilateral tonic-clonic events) in the presence of normal glucose levels. Her EEG revealed left-temporal IEDs. When she was 10 years old, she had an episode of severe SE that required admission to a pediatric intensive care unit. She received several ASMs throughout the course of her epilepsy (Table 1). Even though she achieved prolonged periods of seizure freedom, several attempts to wean her off ASMs were unsuccessful. Additionally, she suffered from psychogenic non-epileptic seizures, which were attributed to social and medical problems.
Patient #3
This female patient was diagnosed with LS at the age of 5.5 years and was one of the first patients diagnosed with LS in Israel. She suffered from frequent hypoglycemic episodes during early infancy and had severe intellectual disability. Her seizures began at the age of 10 in the presence of normal peri-ictal glucose levels. Seizures were frequent and presented as paroxysms of ataxia and recurrent falls, which were well-controlled by ASMs. Several EEGs showed frequent IEDs in the right temporal head region.

Patient #4
This male patient is the brother of patient #3, and was diagnosed with LS at the age of 8 years. He had gait disturbances due to a spine anomaly and cervical myelopathy since early adulthood. Seizures were first documented at the age of 58 years. Seizures were described as focal with impaired awareness, involving the right hemi-body. Soon thereafter, he was hospitalized with an episode of SE. Subsequently, he remained seizure-free on ASMs. His EEG showed right posterior temporal IEDs (Fig. 1). To the best of our knowledge, except the two siblings, no other family members had epilepsy.

Discussion
Our LS cohort consists of 75 individuals followed for up to 57 years, four of whom had epilepsy. This translates to a prevalence of 5.3%, compared with a prevalence of 0.9% in the Israeli population [8]. Seizures among patients with LS have been traditionally regarded as direct or remote sequelae of hypoglycemic episodes known to occur during early childhood [6, 7]. Yet, all glucose levels documented during seizures in this cohort were normal. Furthermore, only 1 patient had documented episodes of hypoglycemia in early childhood.

Fig. 1. Illustrative interictal EEG of patient #4, showing right posterior temporal spikes (traces #7, 8 at 1 and 5 s on double banana montage).
Significant hypoglycemia is known to cause a typical pattern of brain injury that has a distinct predilection for the occipital and sometimes parietal lobes. There are several substantial discrepancies between the epilepsy characteristics that were expected following remote infantile hypoglycemia and those described in this series: (1) Brain MRIs following neonatal hypoglycemia show occipital lobe involvement in up to 90% of cases [9–11]. Yet in our series, none of the 3 patients who underwent a brain MRI demonstrated this characteristic pattern. (2) Epilepsy following remote hypoglycemia is a well-described syndrome [10, 11]. Seizures typically involve visual symptoms. On EEG, the overwhelming majority (70–100%) show occipital or some form of multifocal IEDs. Only 1/41 patients in both series had right temporal IEDs (in the presence of bilateral occipital lesions on neuroimaging). In our series, there were no visual peri-ictal symptoms, and EEG findings in all 4 patients pointed to the temporal lobe rather than the occipital/parietal lobes. Two patients in this cohort suffered at least one episode of SE, one of which (#2) fulfills criteria of medically intractable epilepsy. In the two remaining patients, epilepsy was well controlled on ASMs. While we are unable to determine a clear propensity toward either SE or intractable epilepsy, these patients stress the importance of long-term, specialized neurological follow-up of individuals with LS and seizures.

The important effects of IGF-I during different periods of CNS development have been reviewed by Russo et al. [12]. The IGF-I Receptor signaling pathway is activated from early developmental stages and influences neural cell growth and survival. In Snell dwarf mice, IGF-I distribution in the brain is known to be reduced [12]. Moreover, some neurological manifestations of LS such as brain size and verbal intelligence quotient respond to IGF-I replacement. The above effects of IGF-I treatment on the CNS provide evidence to support the notion that neurological morbidity (such as epilepsy) may be directly linked to the pathogenesis of LS.

**Conclusion**

To the best of our knowledge, this is the first report of epilepsy and SE in a cohort of individuals with LS, in which seizures seem to be unrelated to hypoglycemia. These findings support the view that focal epilepsy may be a distinct neurological comorbidity of LS.

**Statement of Ethics**

This study protocol was reviewed and approved by the Rabin Medical Center Committee, approval number 0612–20-RMC. Written informed consent was not required, as approved by the committee.

**Conflict of Interest Statement**

No author has a potential conflict of interest in this manuscript.

**Funding Sources**

No funding was required for this study.

**Author Contributions**

Dr. Goldberg and Dr. Kraus designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Kraus interpreted the EEG examinations of the patients. Prof. Lar- on conceptualized and designed the study and reviewed and re- vised the manuscript. Prof. Kornreich interpreted brain MRIs of the patients and reviewed and revised the manuscript. Dr. Scheuer- man and Prof. Goldberg-Stern coordinated and supervised data collection and reviewed and revised the manuscript. All the au- thors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**Data Availability Statement**

The data that support the findings of this study are available upon request from the corresponding author (D.K.).
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