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Epilepsy and Amelogenesis Imperfecta: Think of Kohlschütter-Tönz Syndrome

Epilepsi ve Amelogenesis İmperfekta: Kohlschütter-Tönz Sendromunu Düşünün

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Dear editor,

In 2018, an 18-year-old female patient was referred to the adult neurology clinic for history of epilepsy. She had been seizure-free for three years and was not using antiseizure medications (ASM) for two years. When she was 3-month-old, she had a generalized tonic-clonic seizure, although she had no potential risk factors for epilepsy. Her seizures persisted during childhood despite monotherapy with phenobarbital, valproic acid, and oxcarbazepine. At the age of seven, her therapy was switched to levetiracetam (LEV), after which she became seizure-free for 5 years. LEV was discontinued, but then re-started due to seizure recurrence. Four years later, when she was 16 years old, LEV was again discontinued because of seizure-freedom and ASM side effects. Her physical examination disclosed yellow discoloration of the teeth, also known as amelogenesis imperfecta (AI) (Figure 1). Neurological examination revealed moderate mental retardation. Cranial magnetic resonance imaging (MRI) was normal. However routine scalp electroencephalogram (EEG) recording demonstrated spike wave discharges independently over the occipital regions (Figure 2A, B). In 2019, one year after her first admission, she was put on carbamazepine to stabilize her mood and minimize the risk of possible seizures.

The patient was the product of a consanguineous marriage. Her four-year-old younger sister also had epilepsy and AI. Due to epilepsy and AI, a genetic analysis was performed in the Zentrum Medizinische Genetik Innsbruck. The whole coding sequence of the *ROGDI* gene from genomic DNA (exons 1-11, with adjacent intron sequences; reference sequence NM_024589.1) was sequenced after polymerase chain reaction amplification. Findings were consistent with a novel homozygous mutation in the *ROGDI* gene (c.201-1G>T in intron 3). Her sister had the same genetic mutation. They were diagnosed as having Kohlschütter-Tönz syndrome. Both parents were heterozygous carriers for the same mutation.

Kohlschütter-Tönz syndrome is an autosomal recessive syndrome characterized by cognitive impairment, developmental

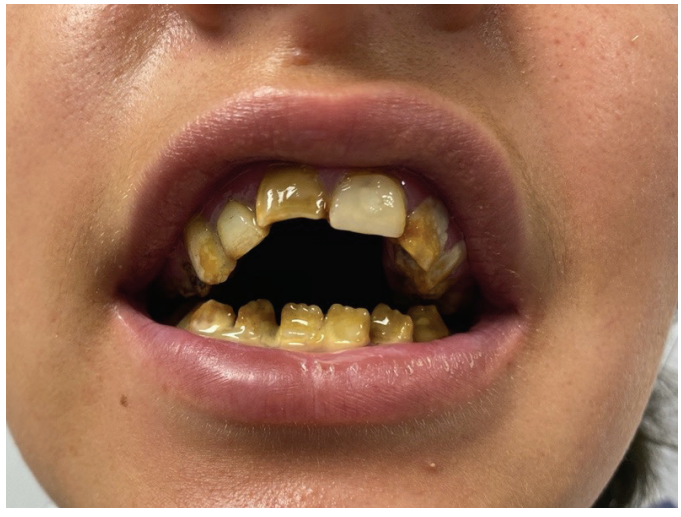

Figure 1. Yellow discoloration of the teeth due to amelogenesis imperfecta

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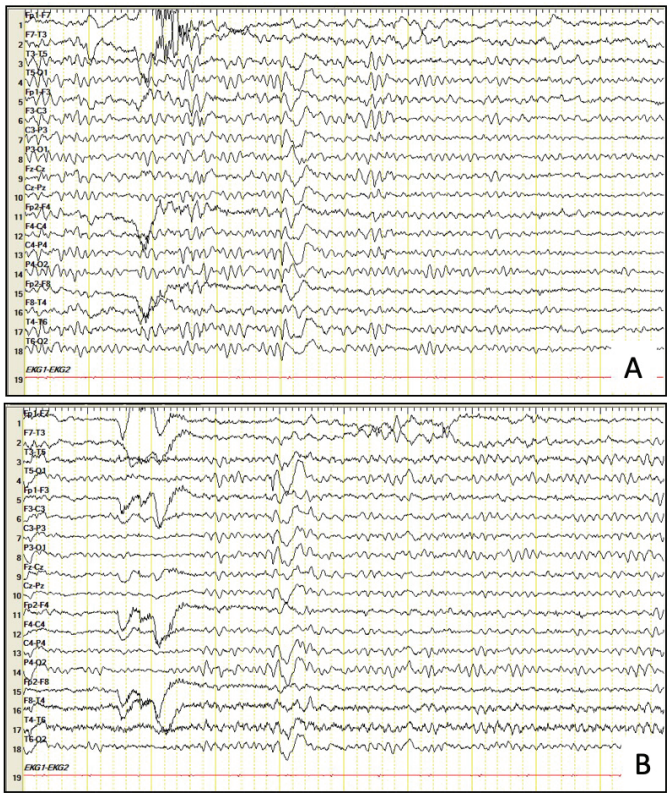

Figure 2. Spike activity that is more prominent either in the right (A) or left (B) occipital area, spreading to homologous regions of the contralateral hemisphere

delay, spasticity, AI, and early onset drug-resistant seizures. The first affected family was reported in 1974 (1). This syndrome occurs because of ectodermal dysplasia. There are no specific clinical and laboratory findings other than characteristic dental changes. The pathophysiological connection between enamel and brain function has not been understood (2,3,4). Clinical course and disease severity may be heterogeneous even within the same family (5). Patients do not possess constant dysmorphic features. There is no characteristic brain involvement, however in some patients, cranial MRI detects ventricular enlargement, cortical atrophy, basal ganglion atrophy, hypoplastic cerebellar vermis, or cerebellar atrophy (3,5). Cerebrospinal fluid (CSF) analysis revealed abnormal concentrations of lactate, glycine, alanine, glutamate, and glutamine in some patients. Nevertheless, CSF showed no appreciable pathology on repeated analyses (3). Non-specific neuronal degeneration was reported in brain biopsy (1). Karyograms are unremarkable.

In 2012, Schossig et al. (2,4) reported mutation in the *ROGDI* gene. This gene's product is highly expressed throughout the brain and other organs. Its function is largely unknown, however recently it has been reported that *ROGDI* is a pre-synaptic protein. The mutation in our patient is presumed to be pathogenic, leading to loss of protein function.

In 2016, the second causative gene for KTS, namely SLC13A5, was reported in four families (4). This gene is highly expressed in the liver and brain. Its protein mediates the utilization of extracellular citrate for fat synthesis in human liver cells (5). Although both *ROGDI* and SLC13A5 have been correlated with epilepsy and AI, there are some variations in their clinical presentation. There are no typical seizure patterns or EEG findings for KTS. Traditionally, seizures have been reported to be drug-resistant; however, their frequency may decrease significantly in adolescence or early adulthood. Seizures may cease altogether, as is evident in our patient. Although cognitive impairment was attributed to severe seizures, improvement in cognitive function was not observed in patients whose seizures were controlled with ASM (2,4).

Until now, less than 50 patients were reported in the literature. Most of them were from Western Europe, with several case reports from South America, United States, India and Israel. Very recently, the clinical and laboratory findings in five Turkish patients were published in different neurological or dentistry journals (5).

To conclude, presentation with impaired cognitive development, epilepsy, and yellow-brown discoloration of the teeth (i.e., AI) should raise the possibility of KTS. Patients should be screened for mutations in the *ROGDI* and SLC13A5 genes. Because of the paucity of affected individuals, there is a lack of longitudinal data. Further patients are needed to better clarify the clinical and genetic characteristics of this syndrome.

Ethics

Informed Consent: Written consent was obtained.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.D., O.S., Concept: N.D., O.S., Design: N.D., O.S., Data Collection or Processing: N.D., O.S., Analysis or Interpretation: N.D., O.S., Literature Search: N.D., O.S., Writing: N.D., O.S.

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