

Kohlschütter- Tönz Syndrome in Siblings without ROGDI Mutation

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Abstract

Background: Kohlschütter-Tönz syndrome is a rare neurodegenerative disorder presenting with intractable seizures, developmental regression, and characteristic hypoplastic dental enamel indicative of amelogenesis imperfecta. Recently, mutations in *ROGDI* were identified in part of Kohlschütter-Tönz syndrome cases, but the siblings reported here do not have a mutation in the *ROGDI* gene, showing that there is genetic heterogeneity in Kohlschütter-Tönz syndrome.

Aim: Report two siblings that have Kohlschütter-Tönz syndrome.

Conclusion: Early onset of seizures and lack of the ability to walk without support may be signs of non-ROGDI mutations in Kohlschütter-Tönz syndrome patients.

Key Words: Epilepsy, Developmental delay, Amelogenesis imperfecta, Kohlschütter-Tönz syndrome

Introduction

Kohlschütter-Tönz Syndrome (KTS) (OMIM# 226750) was first described in 1974 [1] and it is characterized by seizures that are usually treatment resistant, psychomotor delay or regression starting in infancy, spasticity of the upper and lower limbs, and Amelogenesis Imperfecta (AI). Additional manifestations include myopia, ventricular enlargement, vermis hypoplasia, dry skin, and broad thumbs/toes [2-6].

Including this report, 26 individuals in 12 families with KTS have been reported so far in the literature. We report two siblings that have Kohlschütter-Tönz syndrome with early onset seizures but no ROGDI mutation.

Clinical Report

We describe two siblings born to non-consanguineous and healthy parents. The maternal age was 28 and 31, respectively, and the paternal age was 30 and 33 years, respectively. No medical problems were reported in the prenatal period. The mother denied the use of any medications or teratogenic exposure during both pregnancies.

Patient A

The first child, female, is now 14 years old. She was born after 34 weeks of gestation. The pregnancy was normal; however, urinary tract infection triggered labor. She was born at term, by spontaneous delivery, with a birth weight 2 kg, birth height 43 cm, OFC of 43 cm and an Apgar score of 8 and 10. The girl developed mild respiratory distress and was discharged from the hospital after one week. At about 40 days she had the first seizure episode and went into tonic-clonic status epilepticus. She was hospitalized in an intensive care unit for eight days with seizures that were frequent and difficult to control. She was discharged and continued taking phenobarbital and phenytoin at home. However, after one month with no seizures, she developed localized left arm seizures. At 1.2 years of age she began to have atonic seizures controlled with clonazepam. She was hospitalized several times for seizures and was treated with oxcarbazepine, vigabatrin, valproate, and clobazam. Ketogenic diet was prescribed, however with poor results for seizure control.

She sat up independently at 5 years of age and acquired sphincter control at 10 years. Today, at 14 years of age, she is able to walk with help, speaks a few words, and attends the fifth year of mainstream school. Menarche has not occurred yet, however, thelarche and pubarche were observed.

Currently, physical examination does not show dysmorphic features and neurological exams show mild hypotonia. The patient presents marked sialorrhea. She still has seizures and is treated with clonazepam, valproate, acetazolamide, and lamotrigine. She has severe mental retardation, generalized hypotonia, impaired motor coordination skills, ataxia, walks with support, and needs help for all routine daily tasks.

Extensive etiologic investigation included the following: Karyotype, blood and CSF routine biochemistry, urine organic acids, amino acids in blood and urine, acylcarnitine and carnitine profiles, carbohydrate deficient transferrin test, urine sialo-oligosaccharide analysis, dosage of very long chain fatty acids and lysosomal enzymes including arylsulfatase A, hexosaminidase A and total hexosaminidase levels, eye funduscopy, CT scan, and MRI with spectroscopy of the brain. All exams were considered normal. DNA tests were performed to search for mutations on EPM1 gene (mutated in cases of progressive myoclonus epilepsy), DRPLA, mitochondrial DNA disorders, Angelman Syndrome, all with normal results. Rett Syndrome was not considered as a differential diagnosis because seizures started too early, about 40 days after birth, which is uncommon in Rett Syndrome.

The EEG at 45 days of age showed hypersarrhythmia which later developed to left temporal rolandic activity and disorganization of the background. Results at the age of 5 showed a markedly abnormal record due to generalized slowing, spike activity in frontal regions. Additionally, there was significant fast activity. The last EEG was performed in 2011 (14 years old) and showed generalized slowing (slow waves) and irritability in diffuse bilateral rolandic regions (areas of C3 and C4).

Patient B

The second child of the couple is a male who is now 11 years old. Pregnancy was normal and birth was a spontaneous term

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delivery with a birth weight of 3.380 g, height of 49 cm, OFC of 34.5 cm and an Apgar score of 8 and 10. Seizures began at 6 hours of age with episodes of shaking and stiffening accompanied by cyanosis. He was transferred to the intensive care unit and was given oxcarbazepine. Seizures were controlled, however, after 3 months medication was switched to topiramate and valproate. Although he was hospitalized several times to control seizures, they were easier to control than those of his sister.

He crawled at 2 years of age, walked at 6, gained sphincter control at 10 years of age, and has limited speech. Currently, he can talk few words. He is currently treated with topiramate, valproate, and clonazepam controlling his seizures. At the age of 11, he is in the fifth year of mainstream school with difficulties especially in communication skills. Mental retardation is severe (though less than his sister) and he presents ataxia and hypotonia.

Physical examination did not show dysmorphic features, and sialorrhoea was evident. Blood and CSF routine biochemistry were normal, as well as newborn screening for thyroid dysfunction, congenital adrenal hyperplasia, cystic fibrosis, galactosemia, phenylketonuria, aminoacidopathies, biotinidase deficiency and congenital toxoplasmosis. Eye fundoscopy, CT scan and MRI with spectroscopy of the brain were also considered normal. DNA test for Fragile X syndrome and Array-based comparative genomic hybridization were normal.

The EEG at 2 years of age showed spiking activity in the frontotemporal region more frequent on the left. At 10 years the exam presented spike waves and slowing activity in right frontotemporal and left frontal region. The last EEG was performed at 10 years of age.

Dental Aspects in both Patients

Figures 1 and 2, respectively; show the dental aspects of individuals A and B. The siblings, early in life, were monitored, and treated by a specialist in pediatric dentistry. Initially sialorrhoea was observed in both children. There was a marked delay in tooth eruption, and a subsequent delay in the process of exfoliation. Many teeth did not exfoliate and extraction was required. The girl, at age fourteen, still has her primary second molars. The boy did not require surgery to help eruption of permanent teeth, however, his sister required



Figure 1. Intraoral picture of individual A showing several interventions, including covering the crown with dental resin material.

surgery to help eruption of the first permanent molars. Dentition in both siblings, did not present aspects associated with taurodontism, poor root formation, or presence of pulp calcification.

With the aim of treating the lack of enamel, upon eruption of deciduous incisors, several interventions, including covering the crown with dental resin material, were necessary. Enamel of the boy's teeth was thicker. Furthermore, the siblings presented aspects consistent with the presence of alterations found in hypoplastic type amelogenesis imperfecta. Figures 3 and 4 show the panoramic dental radiography of individuals A and B; respectively.

Discussion

Kohlschütter-Tönz syndrome is an inherited disorder dominated by involvement of the nervous system with seizures, progressive spasticity and progressive mental deterioration. An important characteristic found in all reports is amelogenesis imperfecta. Teeth and nervous



Figure 2. Intraoral picture of individual B showing several types of procedures using composite resin to cover the tooth enamel.

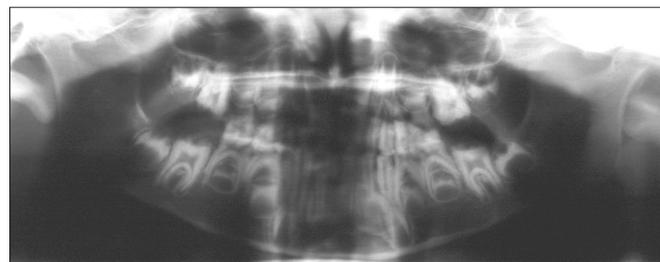


Figure 3. Panoramic teeth radiography of individual A confirming the presence of dental alterations.



Figure 4. Panoramic teeth radiography of individual B confirming the presence of dental alterations.

system develop from the same embryonic origin, and in some ectodermal dysplasias, abnormalities in neurologic development are associated with abnormalities of the skin and of the ectodermal appendages [7,8].

The hereditary defect of enamel, known as amelogenesis imperfecta, occurred in all reports and proved extremely important in helping to characterize this clinical syndrome. Amelogenesis imperfecta occurs as a result of disturbance in tooth formation, beginning at the organic matrix stage and continuing during calcification. It can exist as an isolated feature or in syndromic forms. Inheritance pattern is variable and X-linked and autosomal cases have been detected [9]. Eight different subtypes of amelogenesis imperfecta are described depending on the histology of the tooth. Kohlschütter-Tönz syndrome is usually accompanied by the hypoplastic type [2,4,10], as found in our two patients.

According to Toksavul et al. [11], Laskaris [12], Coffield [13], there may be association of amelogenesis imperfecta with impaction and abnormalities in tooth eruption. Moreover, pulpal calcification, coronary and root resorption, hypercementosis, root malformations and even taurodontism can also be observed. These amelogenesis imperfecta associated features were not observed in our patients, who had only abnormalities of tooth eruption.

According to Santos and Line [14], enamel formation is polygenic, with many proteins interacting in the complex process of growth and mineralization of hydroxyapatite crystals, and this explains different types of amelogenesis imperfecta. Both siblings presented here have alterations found in the hypoplastic type of amelogenesis imperfecta.

Recently, mutations in *ROGDI* were identified in part of

Kohlschütter-Tönz syndrome cases, and in the original cohort used to find the mutated gene, sequencing of *ROGDI* was done in both siblings described in this report [15,16]. DNA samples of the siblings were analysed by Dye-terminator sequencing of all exons and adjacent intron sequences of *ROGDI* (NM_024589.1) (ABI Prism 7000 sequence detection system- Applied Biosystems, Carlsbad, CA and no pathogenic mutation was detected in both affected siblings, contributing to the idea that there is genetic heterogeneity in KTS [15-17].

Comparing the main clinical differences between the two siblings reported here and *ROGDI* gene mutated patients published previously [15-17], we find that:

1) Our patients had earlier onset of seizures. The first episode occurred in patient A at 40 days and in patient B 6 hours after birth. In patients who had the *ROGDI* mutation all but one had tonic-clonic status epilepticus started later than 6 months.

2) Our patients did not acquire the ability to walk without support, and patient A still walks only with assistance. Individuals that had a *ROGDI* mutation walked around 2 years.

Finding the gene(s) mutated in *non-ROGDI* KTS families may bring additional knowledge regarding variability of expression in Kohlschütter-Tönz syndrome.

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