

Treatment of Drop Attacks in Coffin-Lowry Syndrome With the Use of Sodium Oxybate

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Coffin-Lowry syndrome is a well-defined clinical entity classically associated with moderate to severe mental retardation, characteristic facial features, skeletal deformities, and tapering fingers. A characteristic paroxysmal disorder was described in up to 10% patients with Coffin-Lowry syndrome, characterized by sudden loss of muscle tone induced by unexpected tactile or auditory stimuli. These events were given several names, including cataplexy, nonepileptic collapses with atonia, exaggerated startle responses, hyperekplexia, and stimulus-induced drop episodes. Various therapies were undertaken for these drop attacks, including clonazepam, tiagabine, felbamate, selective serotonin reuptake inhibitors, and tricyclics, with variable improvement. We report on a 22-year-old man with Coffin-Lowry syndrome with stimulus-induced drop episodes, who failed therapy with clonazepam, several antiepileptic drugs, and escitalopram, and who was given a trial of sodium oxybate with complete resolution of the drop attacks. © 2007 by Elsevier Inc. All rights reserved.

Havaligi N, Matadeen-Ali C, Khurana DS, Marks H, Kothare SV. Treatment of drop attacks in Coffin-Lowry syndrome with the use of sodium oxybate. *Pediatr Neurol* 2007;37:373-374.

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Introduction

First described independently by Coffin in 1966 and by Lowry in 1971, Coffin-Lowry syndrome is a well-defined clinical entity classically associated with moderate to severe mental retardation, characteristic facial features, skeletal deformities, and tapering fingers in males. Females are much more mildly and variably affected [1]. The inheritance pattern is X-linked. The gene locus was mapped to Xp22.2, and mutations were identified in affected patients in the *RSK-2* gene, a growth factor-regulated protein kinase [2].

A characteristic paroxysmal disorder was described in up to 10% patients with Coffin-Lowry syndrome, characterized by a sudden loss of muscle tone induced by unexpected tactile or auditory stimuli [3,4]. These events were termed cataplexy, nonepileptic collapses with atonia, exaggerated startle responses, hyperekplexia, and stimulus-induced drop episodes.

Various therapies were undertaken for these drop attacks, including clonazepam, tiagabine, felbamate, selective serotonin reuptake inhibitors, and tricyclics, with variable improvement [5]. We report on a 22-year-old man with Coffin-Lowry syndrome with stimulus-induced drop episodes, who failed therapy with clonazepam, several antiepileptic drugs, and escitalopram (a selective serotonin reuptake inhibitor), and was given a trial of sodium oxybate with complete resolution of stimulus-induced drop episodes.

Case Report

A 22-year-old man, born to nonconsanguineous parents as a full-term uncomplicated delivery, was found during childhood to have developmental delay. There was no family history of neurologic illness. Based on his dysmorphic features (hypertelorism, pugilistic nose, coarse facies, large ears, everted lower lip, open mouth, kyphoscoliosis, and fleshy hands with tapering fingers) and an extensive metabolic workup which produced negative results, he was clinically diagnosed as manifesting Coffin-Lowry syndrome at 9 years of age. Genetic testing performed in 2006 by single-strand conformation polymorphism analysis of exon 22 of the *RSK-2* gene did not reveal a mutation. Since age 3 years, he has had generalized tonic-clonic seizures, atypical absences, and infrequent myoclonic jerks. Electroencephalograms disclosed frequent, bilateral, central sharp waves along with diffuse background slowing. The seizures were well-controlled by valproate and clonazepam. At 12 years of age, he began to experience tactile- and auditory-induced episodes of postural loss of tone without loss of consciousness. These episodes increased in

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Received May 3, 2007; accepted June 27, 2007.

frequency and intensity over time, and occurred multiple times daily. Video-electroencephalogram monitoring during several of these episodes did not reveal abnormalities in association with these events. Several other medications, including phenobarbital, levetiracetam, phenytoin, topiramate, lamotrigine, and high-dose escitalopram, were unsuccessful in controlling these episodes. A sleep study showed poor sleep efficiency, sleep-fragmentation with alpha intrusion, and decreased rapid eye movement sleep. The patient was not cooperative enough to perform a multiple sleep latency test. The family refused a spinal tap that had been requested to assay hypocretin levels in the cerebrospinal fluid. Sodium oxybate was gradually introduced at weekly increments, until a final dose of 4.5 g at 10 pm and 2 am was reached. There was complete cessation of these drop attacks within 1 month of achieving the full dose. The patient has been well-controlled at this dose for 1 year, with no further events. The patient experienced vomiting as a side effect of the medication, which was controlled with the use of ondansetron.

Discussion

We present the first case report of successful treatment of stimulus-induced drop episodes in Coffin-Lowry syndrome with the use of sodium oxybate. The patient had typical features of Coffin-Lowry syndrome, although a mutation in the *RSK-2* gene was not detected. Failure to identify a mutation may be related to locus heterogeneity. In a study of 250 cases of Coffin-Lowry syndrome screened by single-strand conformation polymorphism analysis, a mutation was detected in only one third of the patients [6]. Lack of electroencephalogram abnormalities during these episodes excluded epileptic drop attacks, while reduced postural tone, as compared with the increased tone induced by various stimuli during these episodes, along with a lack of response to clonazepam, rendered hyperekplexia an unlikely possibility. Unlike narcolepsy with cataplexy, these episodes were usually not precipitated by emotional triggers [3]. We thus endorse the nomenclature "stimulus-induced drop episodes" for these drop attacks.

Sodium oxybate also known as γ -hydroxybutyrate, is a highly regulated and controlled substance currently approved since 2002 in the United States for the treatment of cataplexy in association with narcolepsy [7]. It increases slow-wave sleep, decreases nighttime awakenings and arousals, and improves sleep efficiency. In adults, it reduces the frequency of cataplexy within 2-4 weeks of initiating therapy. Adverse effects include dizziness, nausea, vomiting, headache, enuresis, anxiety, leg cramps, somnambulism, night terrors, sleep apnea, and early morning awakenings. Sodium oxybate appears to be efficacious in treating the drop attacks associated with Coffin-Lowry syndrome, but it is unclear how it does so. The mechanism may be similar to that involved in the treatment of cataplexy in narcolepsy. Further studies are necessary to validate our observation and to further characterize the treatment of stimulus-induced drop episodes in Coffin-Lowry syndrome.

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