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Stimulus-Induced Drop Episodes in Coffin-Lowry Syndrome^V

Gregg B. Nelson, MD, and Jin S. Hahn, MD

ABSTRACT. *Objective.* Coffin-Lowry syndrome (CLS) is a rare disorder characterized by moderate to severe mental retardation, facial dysmorphism, tapering digits, and skeletal deformity. Paroxysmal drop attacks occur in patients with CLS, characterized by sudden loss of muscle tone induced by unexpected tactile or auditory stimuli. Our objective is to characterize these attacks better using neurophysiologic studies.

Methods. We report 2 teenage boys with CLS and stimulus-induced drop episodes (SIDEs). Simultaneous surface electromyogram (EMG) and video electroencephalogram were performed during SIDEs on our 2 patients.

Results. Both patients had SIDEs stimulated by a loud noise, unexpected light touch stimulation, or visual threat that were characterized by abrupt episodes of complete or partial loss of lower extremity tone. These events were not associated with impairment of consciousness, and immediate recovery was noted. Simultaneous surface EMG and video electroencephalogram revealed no epileptiform discharges in either patient. In the first patient, after unexpected tactile or auditory stimulation, tonic EMG activity in paraspinal muscles was lost briefly, similar to that seen in cataplexy. In the second patient, at 6 years of age, sudden nonepileptic drop episodes were induced by an unexpected tactile, auditory, or visual stimulation. At 11 years of age, his episodes had changed to brief myoclonic jerk and tonic spasm that were triggered by unexpected tactile and auditory stimuli. An increase in tonic EMG activity occurred during the attacks, consistent with hyperekplexia.

Conclusions. Our data suggest that SIDEs in CLS are a heterogeneous group of nonepileptic events that may manifest features of both cataplexy and hyperekplexia, even in the same patient. *Pediatrics* 2003;111:e197–e202. URL: <http://www.pediatrics.org/cgi/content/full/111/3/e197>; *Coffin-Lowry syndrome, drop episodes, nonepileptic events, hyperekplexia, cataplexy.*

ABBREVIATIONS. CLS, Coffin-Lowry syndrome; SIDE, stimulus-induced drop episode; sEMG, surface electromyogram; VEEG, video electroencephalogram.

Coffin-Lowry syndrome (CLS) was independently reported by Coffin et al¹ in 1966 and Lowry et al² in 1971 as a phenotype characterized by moderate to severe mental retardation,

facial dysmorphism, tapering digits, and skeletal deformity. The condition is transmitted by X-linked semidominant inheritance. The gene locus has been mapped to Xp22.2, and mutations have been identified in affected patients in the RSK-2 gene, a growth factor–regulated protein kinase.³

Stimulus-induced drop episodes (SIDEs) have been recently recognized in patients with CLS.^{4–7} These episodes are characterized by a sudden falling that is induced by unexpected tactile or auditory stimuli.^{4–7} These events have been labeled by various names, including cataplexy, nonepileptic collapses with atonia, exaggerated startle responses, hyperekplexia, and drop episodes. The pathophysiology of SIDEs is not well understood. It does not seem to be an epileptic phenomenon, as epileptiform activity was absent during the episodes in all previously reported cases.^{4,5,7} We report our experience in 2 patients with SIDEs in CLS. On the basis of our cases and review of the literature, we suggest that there are diverse mechanisms of SIDEs in CLS.

METHODS

Two patients who had CLS and were referred to the Neurology Clinic at Packard Children's Hospital at Stanford for evaluation of drop episodes constitute our cohort. Event descriptions for both patients were obtained from detailed medical history and a validated cataplexy questionnaire.⁸ With the use of the latter, patients were scored to determine level of cataplexy risk.

Surface electromyogram (sEMG) and video electroencephalogram (VEEG) were obtained simultaneously during SIDEs. The sEMG electrodes were placed over the left lower limb in the quadriceps, hamstring, tibialis anterior, and gastrocnemius muscle. A left lumbar paraspinal muscles electrode was also applied. VEEG was recorded simultaneously using conventional electrodes fixed with collodion, following the International 10–20 system, and recording a total of 14 EEG channels.

Case 1

The patient was born at term via uncomplicated normal spontaneous vaginal delivery to a 33-year-old gravida 1 para 0 woman. During infancy, he was noted to have delay in gross motor milestones and hypotonia. At 23 months, the patient received a diagnosis of CLS on the basis of typical facial and digital features. He continued to have delayed development and hypotonia throughout childhood and at 10 years developed thoracolumbar kyphoscoliosis.

At 13 years of age, he developed SIDEs and sought neurologic evaluation for this problem at 16 years. These events were stimulated by loud noises or unexpected light tactile stimulation that led to a sudden loss of tone with an abrupt drop to the ground usually when standing or walking. They could also be provoked by suddenly waving a hand across his visual field. There was no history of startle or myoclonic jerks. No loss of consciousness was noted, and he was able to recover immediately. SIDEs were not provoked by emotional content or sudden laughter. The events initially had a frequency of 3 to 5 times per year but became more frequent—up to several times per week. Rarely, he injured his face and teeth during episodes. Neurologic evaluation was remarkable

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^V Online version of this article contains video material for Figs 1 and 2. Online version available at: www.pediatrics.org.

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Fig 1. Four frames of video clip showing a typical episode in case 1. In this 16-year-old boy with CLS, an unexpected pull on the shoulders by the examiner leads to a sudden loss of tone with an abrupt drop to the ground. He recovers rapidly, and there is no loss of consciousness (see video clip 1). This brief episode occurs at 00:09 after the start of the clip. The numbers on the bottom left corner of each frame (MM:SS.000) represent the time after the stimulus.

only for low limb tone and a wide-based gait. A SIDE was induced with an unexpected tactile stimulation of the shoulders (Fig 1).

At 17 years of age, a trial of tiagabine at 12 mg/d led to a decrease in severity of SIDEs. His events were described as occurring in "slow motion," which allowed him to generate protective reflexes with his hands.

Case 2

The patient was born to a 23-year-old gravida 1 para 0 woman at term via cesarean section as a result of breech presentation. During infancy, he had hypotonia and delay in motor milestones. Chromosomes were normal. A head magnetic resonance imaging scan was consistent with benign extra-axial fluid collections of infancy. At 5 years of age, he received a diagnosis of CLS on the basis of typical facial and digital features.

At 5 years of age, he developed SIDEs that occurred several times a day. He was noted to lose postural tone in the lower extremities and suddenly drop to the floor after either loud noise or light tactile stimulation. Specific auditory triggers included loud noises such as toilet flushes, yelling, clapping behind his head, opening a door unexpectedly, or the sound of the doorbell. Specific tactile triggers included someone unexpectedly brushing against the patient or touching him from behind. Episodes were also triggered by visual stimuli (eg, by moving a hand across his visual field, moving a hand toward his face). These events occurred while sitting, standing, or walking. No loss of consciousness was noted, and he was able to recover immediately. SIDEs were not provoked by emotion or sudden laughter. Protective reflexes were present during observed episodes but were incomplete. He sustained recurrent injury to his face and chin and knocked out 2 incisors because of the episodes. Neurologic eval-

uation was remarkable for generalized hypotonia and a wide-based gait. EEG was unremarkable.

By 6.5 years, the frequency of SIDEs had increased to 10 to 20 episodes per day and he was placed in a wheelchair for safety. Felbamate was started and titrated to 36 mg/kg/d with a reduction in frequency to 3 to 4 episodes per day. Between 8 and 10 years of age, he was treated with valproate followed by clonazepam, without any significant reduction of SIDEs. Off medication, SIDEs occurred at 5 to 6 episodes per day.

At 11 years of age, the character of the SIDEs changed. They were described as a sudden drop of his head with his arms spreading out laterally as the body lurched forward. These episodes were induced by unexpected auditory and tactile stimuli. A trial of tiagabine at 12 mg/d led to improvement with a reduction in the frequency of events to 3 to 4 events per day (Fig 2). Although he was still able to ambulate, he preferred to use a wheelchair because of SIDEs.

RESULTS

Cataplexy Questionnaire

The validated cataplexy questionnaire⁸ was completed by the patients with the assistance of the parents. The parents were able to provide responses for critical questions, including onset of SIDEs after telling or hearing a joke, laughing, or experiencing anger. Neither patient had an affirmative response to these 3 highly predictive questions. Using a decision



Fig 2. Four frames of video clip 2 showing a typical startle-like episode to sound in our second patient with CLS at 13 years of age. These episodes were triggered by a loud noise and consisted of sudden arm extension and forward lurching of the body (00:41). If they had occurred while he was standing, then he would have fallen to the ground. At 6 years of age, he had a different type of drop episodes. Video clip 2 associated with this case also demonstrates the earlier drop episodes that were triggered by bumping into the furniture while backing up (00:16) or by a pull on his EEG leads (00:26). The numbers on the bottom left corner of each frame (MM:SS.000) represent the time after the stimulus.

tree based on the questionnaire,⁸ both patients fell into the low-risk category for cataplexy (risk: 0.6%).

Neurophysiologic Studies

Case 1

At 16 years of age, simultaneous sEMG/VEEG studies during SIDs did not show epileptiform discharges but demonstrated a brief transient decrease in sEMG activity in the lumbar paraspinal muscles shortly after the stimulus. Decreases in the sEMG activity were also seen in the quadriceps and hamstring muscles. The average latency was 224 msec, and the average duration was 159 msec, followed by an increase in sEMG activity to prestimulus levels.

Case 2

At 6 years, a VEEG captured 3 SIDs unaccompanied by epileptiform activity. SIDs were induced by lightly bumping into furniture or objects as he walked backward and consisted of sudden flexion of the hips with arms following in an extended posture, and rapid falling to the ground. Partial protective reflexes were present, and immediate recovery was noted. At 13 years of age, simultaneous sEMG/

VEEG studies during SIDs did not show epileptiform discharges. Events that were triggered by a loud noise were captured while seated and consisted of sudden forward flexion of the head and upper torso with symmetric abduction of the shoulders and flexion at the elbows. A generalized increase in sEMG activity was present during events consistent with myoclonic jerks with brief tonic spasms during events (Fig 2).

DISCUSSION

A characteristic paroxysmal disorder has been described in patients with CLS, characterized by sudden loss of muscle tone induced by unexpected tactile or auditory stimuli.⁴⁻⁷ These events have been given several names, indicating a poor understanding of their pathophysiology. These names include cataplexy, nonepileptic collapses with atonia, exaggerated startle responses, hyperekplexia, and drop episodes.

One possibility is that SIDs in CLS represent epileptic events. In startle-induced epilepsy, seizures are precipitated by sudden stimuli and are usually tonic or myoclonic in nature.^{9,10} Ictal EEG usually

shows paroxysmal epileptiform activity. However, SIDEs in CLS do not seem to be epileptic in nature, because epileptiform activity is absent during episodes in all reported cases,^{4,5,7} including our 2 cases. Furthermore, startle-induced seizures are generally more prolonged or elaborate than SIDEs.

We reviewed the English literature and found 9 reported cases of "drop episodes" in CLS.^{4-7,11} A comparison of 9 previously reported cases with our cases is presented in Table 1. The mean age of drop episodes onset was 8.6 years. Nine of 11 patients were male. All patients were described as having atonic collapse. In all cases in which details of SIDE was available, the patients experienced sudden giving away of legs from a standing position or during walking with return of normal tone after several seconds. There was no apparent lapse of consciousness during SIDEs. Four reported increasing frequency of episodes with time. Four reported some form of injury to self during events, and 2 of these cases were confined to a wheelchair by the age of 10 years.

Triggers for SIDEs are also presented in Table 1. Auditory triggers were most common, reported in all 8 patients in whom triggers were noted. Tactile triggers and "excitement" were reported in 3 cases each. Visual triggers have not been reported previously but were noted with both of our patients. No cases noted SIDEs induced by laughter or anger or after telling or hearing a joke, common triggers for cataplexy.

Changes in tone with SIDEs were described as instantaneous in all cases. Most of the patients had sudden loss of tone in the lower limbs, rather than myoclonic jerks. Duration of episodes was very short, usually lasting a few seconds in all reported cases. Recovery was immediate in these cases, and

no episodes of more prolonged paralysis were reported (Table 1).

Three of the previously reported cases^{4,5,7} and both of our cases used combined sEMG and EEG studies during SIDEs. None of the 5 patients showed epileptic activity on EEG during SIDEs. Muscles sampled by sEMG included abnormal, paraspinal or quadriceps. Cases 1 and 5 were thought to be consistent with "cataplexy-like" episodes, and cases 2, 4, and 11 were thought to represent exaggerated startle responses or hyperekplexia. Four of these cases had a sudden transient decrease in sEMG activity after stimulus (Table 1). The latency after the stimuli ranged from 60 to 224 ms. The duration of this decreased muscle activity varied from 4 to 159 ms. The latency and duration of decreased activity were somewhat longer in our case 1 than those cases previously reported. This may be attributable to differences in stimuli, recording technique, and patient variability.

Our case 2 was unusual in that during the second decade, the SIDEs evolved from sudden loss of tone ("cataplexy-like" episodes) to sudden increased tone with myoclonic jerks ("hyperekplexia-like" episodes). Neurophysiologic studies during SIDEs at this later stage revealed a generalized increase in sEMG activity in muscles corresponding to a myoclonic jerk. There was no significant latency after stimulus or transient loss of sEMG activity.

SIDEs do not conform well to either hyperekplexia or cataplexy. Table 2 provides a summary of the features differentiating these 2 disorders. Hyperekplexia is defined as an exaggerated motor response to auditory, somesthetic, or visual stimuli that is resistant to habituation and may be characterized by either a brief pathologic startle reflex or a sustained tonic spasm.¹² An appropriate stimulus produces a

TABLE 1. Characteristics of SIDEs in CLS

| Case No. | Authors, Year | Age (Years), Gender | Onset (Years) | Applied Diagnosis | Known Triggers | Neurophysiologic Studies During SIDEs | Treatments and Responses |
|----------|------------------------------------|---------------------|---------------|-------------------|--|---------------------------------------|------------------------------|
| 1 | Present study, 2003 | 16, M | 12 | Cataplexy | Aud, tac, vis | sEMG VEEG: ↓ tone | Tiagabine+ |
| 2 | Ibid | 13, M | 5 | Cataplexy → | Aud, tac, vis | VEEG: nonepileptic | FBM +/-, VPA-, CLN- |
| | | | 11 | Hyperekplexia | Aud, tac | sEMG VEEG: ↑ tone | Tiagabine+ |
| 3 | Padley et al, ¹¹ 1990 | 15, M | ~13 | "Drop attacks" | NA | | |
| 4 | Nakamura et al, ⁴ 1998 | 16, F | 12 | Hyperekplexia* | Aud, tac | sEMG VEEG: ↓ tone | CLN+, VPA-, CBZ-, PB- |
| 5 | Crow et al, ⁵ 1998 | 14, M | 6 | Cataplexy | Aud, electric shocks, excitement, stress | sEMG VEEG: ↓ tone | |
| 6 | Ibid | 10, M | 7 | Cataplexy | Aud | | Clobazam- |
| 7 | Ibid | 35, F | 13 | Cataplexy | NA | | |
| 8 | Fryns et al, ⁶ 1998 | 15, M | 6 | Cataplexy | Aud, excitement | | |
| 9 | Ibid | 14, M | 6 | Cataplexy | Aud, excitement | | |
| 10 | Ibid | 14, M | 4 | Cataplexy | NA | | Scoliosis fusion + |
| 11 | Caraballo et al, ⁷ 2000 | 16, M | 11 | Hyperekplexia* | Aud | sEMG VEEG: ↓ tone | CLN and LMT -, clomipramine+ |

Aud indicates auditory; tac, tactile; vis, visual; NA, not available or mentioned; FBM, felbamate; VPA, valproic acid; CLN, clonazepam; CBZ, carbamazepine; PB, phenobarbital; LMT, lamotrigine; +, reduction or elimination of SIDEs; +/-, transient response; -, no significant response.

* "Hyperekplexia-like" episodes or exaggerated startle responses.

TABLE 2. Features Differentiating Hyperekplexia, Cataplexy, and SIDs

| | Hyperekplexia | Cataplexy | SIDs |
|----------------------------|---------------|--------------------|---------------------------|
| Trigger | Physical | Emotional | Auditory, tactile, visual |
| Tonal change during attack | Increased | Decreased | Usually decreased |
| Partial tone loss | No | Possible | No |
| Brief paralysis | No | Possible | No |
| Protective reflexes | No | Possible | Possible |
| Duration of event | Seconds | Seconds to minutes | Seconds |
| Recovery | Immediate | May be delayed | Immediate |
| Treatment | VPA, CLN | TCA, SSRI | CLN, tiagabine |

CLN indicates clonazepam; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.

sudden stereotyped shock-like movement usually involving facial grimacing; abduction of the shoulders; and flexion of the neck, trunk, elbows, and knees. Consciousness remains intact during episodes, and most patients are able to rise immediately. Patients with sustained tonic spasm are reported to fall rigidly to the floor, unable to take protective action, resulting in self-injury.¹³ Cataplexy, an ancillary symptom of narcolepsy, is defined as the sudden loss of bilateral muscle tone that is more pronounced in the antigravity muscles and is provoked by a strong emotion with preservation of consciousness lasting less than a few minutes.¹⁴ The most common emotional expression that provokes cataplexy is laughing, which is reported to be the trigger in >80% of cases. Other common precipitants include anger, fear, surprise, and excitement. In most patients, cataplexy lasts for 1 minute or less. Closure of the eyes, sagging of the jaw, slurred speech, nodding of the head, dropping of the arms, and giving way of the knees are characteristic. Loss of muscle tone may be partial and is not always instantaneous but can progress over a few seconds and spread from cranial muscles to upper and lower limb muscles. In these cases, patients may be able to mount a protective response. Only approximately one third of patients with cataplexy experience sudden and severe loss of muscle tone causing collapse to the ground.¹⁴ During these episodes, the patient cannot move the extremities. Muscle hypotonia and decreased or abolished muscle stretch reflexes are noted, whereas eye movements and sometimes verbal communication are possible.⁸

The typical triggers that induce hyperekplexia (sudden unexpected auditory or tactile stimuli) were also found in the majority of our patients with SIDs. However, in hyperekplexia, the stimuli are followed by a shock-like jerk (increased tone) rather than a loss of muscle tone. Hence, the sudden loss of tone in SIDs more closely resembles the motor response in cataplexy. Only 1 patient (case 2) had sEMG-documented myoclonic or shock-like jerks after stimuli. Episodes in cases 4 and 11 were considered as hyperekplexia-like but in fact were accompanied by loss of tone rather than increased tone on sEMG. The typical triggers of cataplexy (elation, laughter, and anger) that are the most sensitive indicators for identifying cataplexy⁸ were not reported in any case of CLS.

The duration of the SIDs in CLS is much shorter than typical cataplexy. All cases reported SIDs that were of no more than several seconds in duration. In

cataplexy, the majority of cases are less than 1 minute in duration but usually longer than a few seconds. Approximately 27% of cases of cataplexy are of a longer duration (>1 minute).¹⁴

Various therapies were used for SIDs for 5 of 11 patients (Table 1).⁴⁻⁷ Rarely, near-complete improvement of symptoms has been reported with the use of clonazepam (case 4) and clomipramine (case 11). It is interesting that complete resolution of SIDs was noted after scoliosis fusion surgery in 1 patient (case 10). We treated both of our patients with tiagabine because it is a potent GABA-uptake inhibitor that enhances neuronal inhibition. In case 1, a reduction in the severity of SIDs was observed. In case 2, a reduction of SIDE frequency was noted. However, in neither case was the response to tiagabine dramatic. Conventional antiepileptic medications including valproic acid, carbamazepine, phenobarbital, and lamotrigine have been generally ineffective in the treatment of SIDs.

Case 2 was the only one that seems to manifest signs and symptoms of true hyperekplexia with confirmation on sEMG. Episodes in other cases (4 and 11) labeled as "hyperekplexia-like" demonstrated loss of tone during SIDs. However, case 2 had also previously experienced documented atonic SIDs 8 years earlier. Although no case fulfilled the criteria for cataplexy, case 6 was considered to have "cataplexy-like" episodes because of the abrupt loss of tone from the head downward and successful voluntary attempts to overcome attacks.

Proposed neurotransmitter mechanisms differ in hyperekplexia and cataplexy. Hyperekplexia is believed to be mediated by reduced glycine receptor sensitivity leading to reduced glycinergic inhibition in the spinal cord and subsequent neuronal hyperexcitability.¹⁵ In cataplexy, hypersensitivity of the muscarinic cholinergic system has been postulated to be the mechanism.¹⁴

In regard to structural localization, it has been suggested that hyperekplexia is mediated by pathways concentrated in the pontomedullary reticular formation,¹⁵ whereas cataplexy has been proposed to be mediated by pathways concentrated in the mediodorsal pontine tegmentum.¹⁴ Given the proximity of suspected localization of neuronal circuitry in these 2 conditions and the unusual characteristics of case 2 in which a change in tonal characteristics of SIDs occurred over time, the possibility exists that these conditions may involve parallel neuronal pathways allowing shifting expression of tonal control through pontomedullary reticular neurons.

CONCLUSION

SIDEs in CLS are nonepileptic events usually characterized by atonic collapses triggered by sudden stimuli with immediate and complete recovery. Although there are similarities to hyperekplexia and cataplexy, SIDEs have a distinctive pattern of features (Table 2). Given the lack of characteristic emotional triggers, the reliably short duration of events, and the presence of immediate recovery in all cases, SIDEs should not be classified as cataplexy. Combined VEEG and sEMG recordings of SIDEs demonstrate that a brief loss of tone in the paraspinal or quadriceps muscles is characteristic in the majority of cases. Finally, we report a single case that demonstrates evolution of tonal characteristics over time and not only suggests that SIDEs may have the potential for evolution over time but also provides a possible explanation for the broad range of previously reported presentations.

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