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Review

Stimulus-induced drop episodes in Coffin–Lowry syndrome

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ABSTRACT

The Coffin–Lowry syndrome (CLS) is a rare but well-defined X-linked semidominant syndrome characterized by psychomotor and growth retardation, and progressive skeletal changes. CLS is caused by loss of function mutations in the Rps6ka3 gene encoding the ribosomal S6 kinase 2 (RSK2) protein. A distinctive paroxysmal disorder has been described in some CLS patients, characterized by episodes of sudden falling, without apparent alteration of consciousness, usually induced by unexpected tactile or auditory stimuli. Duration of episodes is very short, usually lasting a few seconds. The appellation "Stimulus-induced drop episodes" (SIDEs) was proposed for these non-epileptic events in CLS patients. SIDEs are clinically heterogeneous; with some patients exhibiting cataplexy-like events characterized by sudden hypotonia and collapse, and others hyperekplexia-like episodes with a startle response. The pathophysiology of SIDEs is not well understood.

1. Introduction

Coffin–Lowry syndrome (CLS) was independently reported by Coffin et al. in 1966 and Lowry et al. in 1971 as a phenotype characterized by moderate to severe mental retardation, facial dysmorphism, puffy proximal digits, tapering digits, and skeletal deformity [1]. The condition is transmitted by X-linked semidominant inheritance. Female carriers show variable partial manifestation of the disease. The gene locus has been mapped to Xp22.2, and highly heterogeneous loss of function mutations have been identified in affected patients in the *RPS6KA3* gene encoding the RSK2 protein kinase [2]. RSK2 acts at the distal end of the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathway, and is activated by serine/threonine phosphorylation in response to many growth factors and neurotransmitters [3].

2. Stimulus-induced drop episodes (SIDEs)

A distinctive paroxysmal disorder has been described in patients with CLS, characterized by episodes of sudden falling that are usually induced by unexpected tactile or auditory stimuli [4–8]. These events have been given several names including "cataplexy," non-epileptic collapses with atonia, exaggerated startle responses, hyperekplexia, and drop episodes. We coined the term "Stimulus-induced drop episodes" (SIDEs) in 2002 because it did not imply any mechanisms or pathophysiology [8]. (We had considered stimulus-induced drop attacks, but the acronym would have been "SIDA," which is the Spanish acronym for AIDS; therefore, we chose SIDEs instead.).

2.1. Epidemiology

SIDEs have an onset between the ages 4 and 17 and a mean age of onset of 8.6 years [8–12]. The overall prevalence is approximately 10–14% [5]. Data from the CLS Foundation's database revealed a higher overall prevalence of 20% and a peak prevalence of 21–27% between ages of 10–20 [10]. It should be mentioned that, although the majority of reported cases with SIDEs appear to be male, about one-third are female cases (7/22) [4,8–12].

2.2. Clinical characteristics of SIDEs

SIDEs are usually characterized by sudden loss of muscle tone induced by unexpected tactile or auditory stimuli. Fryns et al. [13] reported two brothers with CLS who were thought to have generalized epilepsy. However, in a long-term follow up study [5], they were found to have non-epileptic events as evidenced by the lack of epileptiform discharges on the electroencephalograms (EEG). Crow et al. [4] also reported similar non-epileptic collapse with atonia in

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two males and one female. Their episodes were also precipitated by loud noise or excitement.

Since then several reports have described similar episodes in patients with CLS and have provided more detailed descriptions and clinical neurophysiological data [6–8,10]. These studies have shed some light on the pathogenesis of SIDEs. In these reports, all patients were described as having drop episodes or atonic collapse. The sudden loss in tone was instantaneous, and involved the lower limbs. The patients experienced sudden giving away of legs from a standing position or during walking, with rapid return of normal tone. Duration of episodes was very short, usually lasting a few seconds. There was no apparent alteration of consciousness during SIDEs. No episodes of more prolonged paralysis have been reported.

Auditory triggers were most common, reported in virtually all reported cases [4,6–8,10,11]. Tactile stimulation induced episodes in three [6,8] and "excitement" in three [4,5]. Sudden visual stimulation, such as hand waving suddenly in the visual field was noted in two patients [8].

2.3. Clinical neurophysiology

Several studies have utilized combined surface electromyogram (sEMG) and video EEG studies during SIDEs [4,6–8]. None of the patients showed epileptic activity on EEG during SIDEs. In four of the five cases, there was a sudden transient decrease in sEMG activity in the abnormal, paraspinal or quadriceps muscles after the stimulus that caused the SIDE. The latency after the stimuli ranged from 60 to 224 ms. The durations of the decreased muscle activity varied from 4 to 159 ms. The sudden decrease in muscle activity during a SIDE suggests that the mechanism may be related more to cataplexy rather than hyperekplexia (see below).

One patient, who had atonic spells as a child developed startle-like jerks during his second decade, showed a different pattern on sEMG. There was an increase in muscle tone during the myoclonic or shock-like jerks after stimuli [8]. Two other cases were considered as hyperekplexia-like, but in fact, were accompanied by loss of tone rather than increased tone on sEMG [6,7].

EEG studies showed absence of epileptiform activity during SIDEs in CLS [4–8]. There was also no disruption of the background and a normal awake EEG pattern precedes the SIDE and reemerges immediately after it. Although during the episodes muscle artifacts may obscure the EEG, the lack of background alteration surrounding the event and post-event slowing provide evidence that these are not epileptic events.

2.4. Comparison to cataplexy, hyperekplexia, and startle epilepsy

SIDEs share some characteristics of cataplexy, a symptom of narcolepsy. *Cataplexy* consists of 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]. A cephalo-caudal spread of atonia typical of cataplexy has been reported in some individuals with SIDES [4]. The duration of the SIDES is shorter than that of cataplexy. Laughter is the most common trigger provoking cataplexy and is seen in more than 80% of cases, but is not a common trigger of SIDEs. Only one reported case has noted SIDEs that were triggered by laughter or telling a joke [10], a common triggers for cataplexy associated with narcolepsy. Catapletic attacks have a longer durations than that of SIDEs, usually a few seconds to a minute [14].

Hyperekplexia is defined as an exaggerated motor response to auditory, somaesthetic or visual stimuli, and is characterized by either a brief pathologic startle reflex or a sustained tonic spasm [15]. The stimulus produces a sudden stereotyped shock-like movement usually involving facial grimacing, abduction of the shoulders, and flexion of the neck, trunk, elbows and knees. Consciousness is preserved during episodes and most patients are able to rise immediately. The typical triggers that induce hyperekplexia (e.g., sudden unexpected auditory or tactile stimuli) were also present in the majority of the patients with SIDEs.

Hyperekplexia-like SIDEs could easily be mistaken for *startle-induced epilepsy*. However in this epileptic syndrome, the seizures are precipitated by sudden stimuli and consist of tonic posturing or myoclonic movements, rather than atonia [16,17]. These seizures are usually associated with electrodecremental responses, generalized spike-wave, or polyspike discharges, although sometime no surface EEG correlates are seen [16,17]. The EEG during hyperekplexia-like SIDEs does not show epileptiform activity.

2.5. Epilepsy in CLS

Approximately 5–30% of CLS patient may have true epileptic seizures in addition to SIDEs [10,18,19]. Seizures often appear to have a focal onset and involve tonic posturing and clonic movements and are longer in duration than SIDEs.

2.6. Natural course of SIDEs

There appears to be a range of motor manifestations in CLS and individual patients may have more than one type of spells [8,10]. One patient who had SIDEs with sudden loss of tone (cataplexy-like episodes) during the first decade developed startle-induced myoclonic jerks (hyperekplexia-like episodes) during the second decade [8]. Neurophysiologic studies during SIDEs at this later stage revealed a generalized increase in sEMG activity in muscles corresponding to a myoclonic jerk. Another patient in the same series developed hyperekplexia-like startle episodes with tonic arm extension in his early 20s, which were at time severe enough to knock himself out of his wheelchair (unpublished observation). Stephenson et al. [10] have also emphasized that there may be a variety of movement disorders in CLS. As a case in point, they described female with CLS who had sound-induced drop attacks during first decade, cataplexy involving neck and trunk muscles induced by telling a joke, and prolonged startle hypertonia (hyperekplexia-like episodes). There appears to be age-dependent expression with cataplexy-like SIDEs (i.e., atonic falls) being more common in younger children and hyperekplexia-like SIDEs (i.e., myoclonic jerks or tonic spasms) during second or third decade [8,10].

The frequency and severity of SIDEs seems to increase with age [5,8]. The falls often become a debilitating complication of CLS due to injury to self during the events [8]. Most of the children with SIDEs end up in a wheelchair to reduce injury [8,10].

2.7. Management of SIDEs

Various therapies have been utilized for SIDEs. They include antiepileptic agents (e.g., lorazepam, clobazam, tiagabine, felbamate, valproic acid, carbamazepine), selective serotonin reuptake inhibitors (e.g., fluoxitine and escitalopram), and tricyclics (e.g. clomipramine) [4–8,11]. Benzodiazepines are often used as a first-line treatment. Rarely near complete improvement of symptoms has been reported with the use of clonazepam [9]. Conventional antiepileptic medications including valproic acid, carbamazepine, phenobarbital, and lamotrigine have been generally ineffective in the treatment of SIDEs. Valproic acid use was reported in a 28-year-old male and reduced the number of episodes in a dose dependent manner [20]. Fluoxitine has been used in one female case with a significant reduction of SIDEs [11]. Clomipramine has also been noted to be efficacious [7]. However, most of these treatments have not resulted in significant long-term control of SIDEs.

Sodium oxybate has recently been used to treat a 22-year-old male with success [18]. This medication is also known as γ-hydroxybutyrate (GBH) and has an approved indication in United States for the treatment of cataplexy associated with narcolepsy. The mechanism of how it inhibits SIDEs is not clear, but may be similar to that involved in reducing cataplexy in narcolepsy [18].

Interestingly, complete resolution of SIDEs was noted after scoliosis fusion surgery in one patient [2], although one of the authors' patient did not benefit from such surgery.

Peripheral muscle weakness and atrophy have been noted in CLS [4,10]. Children with CLS have been noted to have abnormal muscle echogenicity on ultrasound examinations [4]. Muscle biopsies and electrophysiologic studies have not shown a consistent pattern [4,21]. The exact nature of the neuromuscular dysfunction has not been well characterized.

2.8. Mechanism of SIDEs

The underlying mechanism of the SIDEs in CLS is unknown. In cataplexy, hypersensitivity of the muscarinic cholinergic system has been postulated as the mechanism [14]. Cataplexy has been proposed to be mediated by pathways concentrated in the mediodorsal pontine tegmentum [14]. Hyperekplesia can result from mutations in genes encoding various postsynaptic proteins involved in glycinergic neurotransmission, including the glycine receptor α1 (*GLRA1*) and β (*GLRB*) subunits, gephyrin (GPHN) and collybistin (*ARHGEF9*), but also in the *SLC6A5* gene encoding the presynaptic glycine transporter GlyT2. Therefore, hyperekplexia is believed to be due to defective inhibitory glycinergic transmission in the spinal cord, and subsequent neuronal hyperexcitability [22]. Pathways concentrated in the pontomedullary reticular formation [23] mediate hyperekplexia. Based on these observations, the area of neurotransmitter dysfunction that causes SIDEs may be to be in the rhombencephalon.

The Rps6ka3 knockout mouse (*mrsk2*-KO) exhibits no brain abnormality at the anatomical and histological levels. At the behavioral level they display learning and long-term spatial memory deficits [24]. Although, there is no SIDES and epilepsy in *mrsk2*-KO mice, they exhibit hyper-responsiveness toward changes in the environment. An increased level of cortical dopamine was found in *mrsk2*-KO mice that may be suspected to play a role [25].

2.9. Molecular genetics

RPS6KA3 is the only gene known to be associated with CLS [26]. Over 150 distinct inactivating mutations have so far been identified in CLS patients. Mutations are distributed throughout the gene and the vast majority is unique to a single family. Approximately 30% of mutations are missense mutations, 15% nonsense mutations, 20% splicing errors, and 30% short deletion or insertion events [27]. No consistent relationship has been observed between specific mutations and the severity of the disease or the expression of particular features [28]. Nakamura et al. [9] suggested that truncating mutations disrupting the N-terminal kinase domain may cause a susceptibility to SIDEs, but Jurkiewicz et al. [12] reported a patient with SIDEs and carrying a missense mutation.

3. Conclusion

SIDEs in CLS are non-epileptic events usually characterized by atonic collapses triggered by sudden stimuli with immediate and complete recovery. While there are similarities to hyperekplexia and cataplexy, SIDEs have a distinctive pattern of features. Some patients have cataplexy-like events characterized by sudden hypotonia and collapse, while others have hyperekplexia-like episodes with a startle response. Combined video EEG 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, there may be evolution of the 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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