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Original article

The movement disorders of Coffin–Lowry syndrome☆

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Abstract

Coffin–Lowry syndrome (CLS) is an X-linked semi-dominant condition with learning difficulties and dysmorphism caused by mutations in the gene *RSK2*. Originally, epilepsy was reported as a feature. We and others have since described predominantly sound-startle induced drop attacks that have been labelled 'cataplexy', abnormal startle response and hyperekplexia. We sought to clarify why there should be controversy over the type of paroxysmal events. Review of the literature and our patients confirmed that each centre had studied only a small numbers of individuals (mean = 2). The type of movement disorder varied both with age and between individuals. One individual might have more than one movement disorder. One of our adult patients had several types of movement disorder and epilepsy that merged seamlessly: there was true cataplexy triggered by telling a joke, something close to cataplexy ('cataplexy') triggered by sound-startle, a predominantly hypertonic reaction varying from hyperekplexia to a more prolonged tonic reaction resembling startle epilepsy, and true unprovoked epileptic seizures. In the large database of the Coffin–Lowry Syndrome Foundation family support group, 34 of 170 (20%) individuals with CLS and known age had 'drop attacks' and an additional 9 (5%) of these had additional epileptic seizures. The onset of such events was usually after age 5 years, prevalence peaking at 15–20 years (27%). Many became wheelchair bound as a result. This unique combination of more than one non-epileptic movement disorder and epilepsy deserves further semiological and genetic study both for the patients with CLS and for the wider implications.
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Keywords: Coffin–Lowry syndrome; Cataplexy; Hyperekplexia; Movement disorders; Startle epilepsy and epilepsy

1. Background

Coffin–Lowry syndrome (CLS) is an X-linked semi-dominant condition with dysmorphism and cognitive difficulties, more severe in affected males, due to mutations in the *RSK2* protein kinase gene. The expression of this *RSK2* gene has been mapped in human and mouse brain and reported to be prominently expressed in brain structures essential for cognition and learning [1]. It has recently become clear that an important neurological complication of CLS is some form of drop attack, beginning on childhood (see Box for definitions of neurological terms).

Earlier reports of the clinical features of CLS included descriptions of what the authors called epilepsy or epileptic seizures [2,3], but only recently has the nature of these paroxysmal attacks been questioned. As is often the case, several groups of clinicians and investigators noticed something novel at about the same time. The Glasgow group was the first to publish a peer-reviewed article on 'cataplexy' in three patients with CLS [4]. Previous to that, the Glasgow school with other colleagues had presented their material at a meeting of the European Paediatric Neurology Society [5] at which Jean Aicardi drew

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Definitions of neurological terms

Movement disorders. Commonly refers to paroxysmal disorders of movement that do not have an epileptic basis. Examples relevant to this paper include hyperekplexia and cataplexy.

Startle reaction. The normal reaction to a surprising stimulus is a sudden increase in muscle tone, and a pathological startle reaction as in hyperekplexia involves gross increase in muscle activity. Some authors have included sudden loss of tone in their definition of pathological startle reaction.

Hyperekplexia. Otherwise called startle disease, this is usually manifest as pathological startle reactions with sudden gross increase in muscle tone due to a genetic defect in a subunit of the inhibitory glycine receptor.

Cataplexy. Sudden loss of muscle tone resulting from strong emotion is common in narcolepsy, otherwise called narcolepsy–cataplexy. The emotional trigger is usually laughter such that cataplexy occurs either when hearing a joke or telling one. The loss of tone has a cephalo-caudal progression, beginning in and sometimes only present in the muscles of the face and neck.

'Cataplexy'. Quotes 'cataplexy' is a term we and others have used for collapse that includes sudden loss of tone but in which there are features atypical for cataplexy. Such features include sound-startle as the predominant stimulus, lack of strong emotion as an intermediary between the stimulus and the response, and lack of a cephalo-caudal progression of the atonia (for example, isolated buckling of the legs).

Epilepsy. Epilepsy implies a tendency to recurrent epileptic seizures. Traditionally, epileptic seizures are subjective or objective changes in behaviour due to sudden changes in the electrical activity of the brain. Epileptic seizures with a bilateral motor component, even if that involves a sudden loss of muscle tone as in atonic epileptic seizures or in so-called negative myoclonus, are usually accompanied by high voltage electrical discharges sufficient to be seen on surface EEG recordings.

Startle epilepsy. In this form of epilepsy some of the epileptic seizures are induced by startle such as a sudden sound or unexpected touch. Commonly these seizures, which are often tonic, that is characterised by prolonged sustained increase in muscle tone, are not accompanied by visible scalp EEG discharges.

the attention of the presenters to an abstract [6] for the forthcoming Child Neurology Society (CNS) meeting. One of the Glasgow group (JBPS) then went to the CNS meeting in Phoenix, Arizona to see this poster on hyperekplexia in CLS [6]. We agreed to differ as to the type of movement disorder. Very shortly afterwards, a report from Japan [7] called the drop attacks exaggerated startle response. Table 1 summarises all the available published data [2–4,6–13]. The small number of patients with CLS and epilepsy or movement disorders studied by each author is remarkable (mean 2, mode 1, range 1–4).

Table 1
Publications on 'epilepsy' and movement disorders in Coffin–Lowry syndrome

Reference	Description of movement disorder	Number of patients/gender
Fryns et al. [2]	Epilepsy	2/M
Padley et al. [3]	Epilepsy	1/M
Crow et al. [4]	'Cataplexy'	2/M, 1/F
Fryns and Smeets [8]	'Cataplexy'	3/M, 1/F
Fryssira et al. [9]	'Cataplexy'	1/F
Cheyette et al. [6]	Hyperekplexia	4/M
Nakamura et al. [7]	Startle response	1/F
Caraballo et al. [10]	Startle response	1/M
Stephenson [11]	Mixed	1/F
Hunter [12]	Mixed	2/M
Nelson and Hahn [13]	Mixed	2/M

Ref. [8] includes the patients in Ref. [2].

2. Clinical observations

We have made some further clinical observations and video recordings on two further individuals with CLS known to us.

2.1. Case 1

Pure atonic falls have been observed by R.C.B. in a boy from England and subjected to slow motion video. These differed from the *classical* cataplexy of narcolepsy–cataplexy [14] in that the sound startle induced atonia was predominantly in the lower limbs (Fig. 1) and was not laughter related as in cataplexy proper [14]. Coffin–Lowry syndrome having been diagnosed at the age of 3 years, his drop attacks began at age 7 and were initially always triggered by an unexpected loud sound. Later aged 10 years some appeared to be unprovoked. He also had two right-sided partial epileptic seizures aged 8 years. His Coffin–Lowry syndrome is severe in that he requires tube feeding via a gastrostomy, but his mental retardation is judged only moderate. *RSK2* mutations have not been looked for.

2.2. Case 2

This is the patient previously described in abstract [11]. She has fully manifest CLS, her typical physical appearance having been confirmed at a Dysmorphology Group meeting

Fig. 1. Boy in Case 1. Immediately a balloon is burst behind him his knees buckle atonically and he falls on his bottom.

at The Hospital For Sick Children, Great Ormond Street, London in 1984 when she was aged 15 years. Subsequently, the *RSK2* mutation R110X was identified. Although she has substantial cognitive impairments, her verbal ability is good. She began to have drop attacks aged about 6–7 years but the provoking effect of sudden unexpected sounds was only realised when she was aged 16. Her episodes have evolved over the years and now include true cataplexy (Fig. 2A and B), something akin to what we called 'cataplexy' [4] with a suggestion of hyperekplexia (Fig. 3A and B), prolonged startle hypertonia of unidentified

Fig. 2. (A) Woman in Case 2. She is telling a joke. (B) There is immediate loss of tone in her neck extensors with head drop and passive flexion of the trunk.

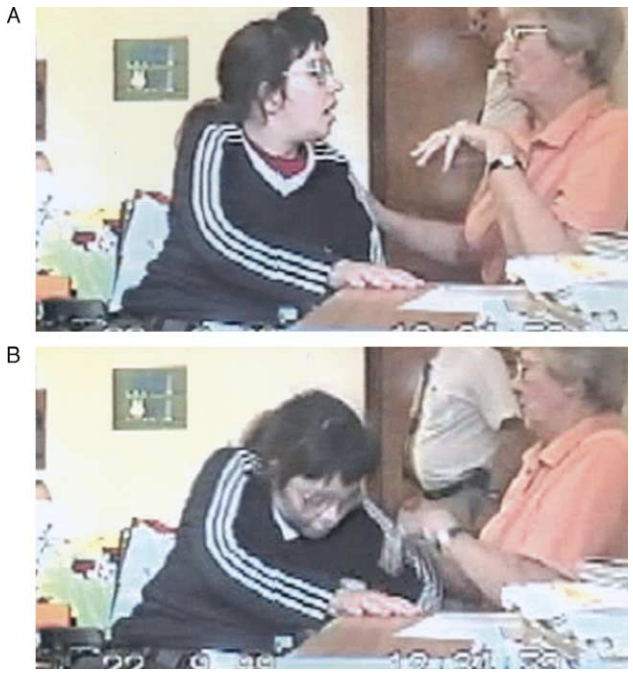

Fig. 3. (A) Same patient in this and succeeding figures. While she is in conversation with her mother, the first author slams the door. (B) Immediate startle with brief contraction of the elevators of her shoulders and truncal collapse.

mechanism (Fig. 4A–E), and unprovoked nocturnal epileptic seizures that begin with a semiology similar to the startle disorder just described, but continue as clonic epileptic activity for 2 min (Fig. 5A and B, Table 2).

3. Epidemiological observations

One of us (MH) started the Coffin–Lowry syndrome Foundation (CLSF) as a support group in 1991 after her son was diagnosed with CLS. Families of those diagnosed as CLS by a physician or geneticist make contact via the web site. Of 265 affected individuals on the CLSF database, 8 have a confirmed *RSK2* defect, 5 do not, and the remainder have a clinical diagnosis of CLS.

Table 3 gives the age distribution of those on the database with known age, both with and without a history of drop attacks. From this, it appears that drop episodes tend to begin over the age of 5 years with a maximum prevalence of 21–27% in the 10–20 age groups, and an overall prevalence of 20%.

It is the impression of the organizer that most of those so affected end up in wheel chairs, but quantitative data are not available.

The detailed description of the type or types of drop attack is mostly not yet available. Of those whose age is known, 9 (5%) have additional epileptic seizures but further details of these are also not yet available.

Fig. 4. (A) She is listening to her mother. The large hands with characteristic tapering fingers are evident. (B) The immediate response to a sudden unexpected loud shout. She appears to be quivering violently, albeit transiently. (C) Elevation and extension of her left upper extremity is the first manifestation of sustained hypertonia. (D) In the succeeding seconds her upper limb postures vary, and her facial appearance suggests considerable misery. (E) There is a further elevation and extension of her left upper limb before the episode of hypertonia concludes.

4. Discussion and future proposals

The mechanisms of the movement disorders of Coffin–Lowry syndrome have been controversial. It seems that there are four reasons for this. One is that the movement disorder varies from individual to individual, so that one may have something more like cataplexy and another something more like hyperekplexia (Table 1). Secondly, more than one movement disorder may be present in the same individual with CLS [11,13] as in the patient in Case 2 in the present paper. Thirdly, the movement disorder may change with time [13] such that very prolonged observation may reveal multiple paroxysmal phenomena as in the patient in Case 2. Finally, it is not only a question of deciding whether an individual with CLS has epilepsy or a movement disorder, he or she may have *both* as in our two cases. Indeed, and of great interest to those involved in either the study of movement disorders or of epilepsy, the patient in Case 2 has presented with an almost seamless transition between cataplexy, 'cataplexy', hyperekplexia, something akin to startle epilepsy [15] and spontaneous epileptic seizures of possible 'partial' onset.

The movement disorders of CLS are common and seriously disabling. This evidence, together with the great scientific interest from the point of view of movement disorders and epilepsy merits further study beyond isolated case reports. Only a small minority of all CLS patients have been genotyped. Different types of mutation have been described and are distributed throughout the *RSK2* gene without obvious clustering or phenotypic association, except some missense mutations are associated with a milder phenotype [16]. Interestingly, Fryssira et al. [9] also described a fully affected female who, at the age of 9 years, had onset of a cataplexy-like phenomenon characterized by a sudden and reversible loss of muscle tone without loss of consciousness. The mutation in this case was an A-to-G

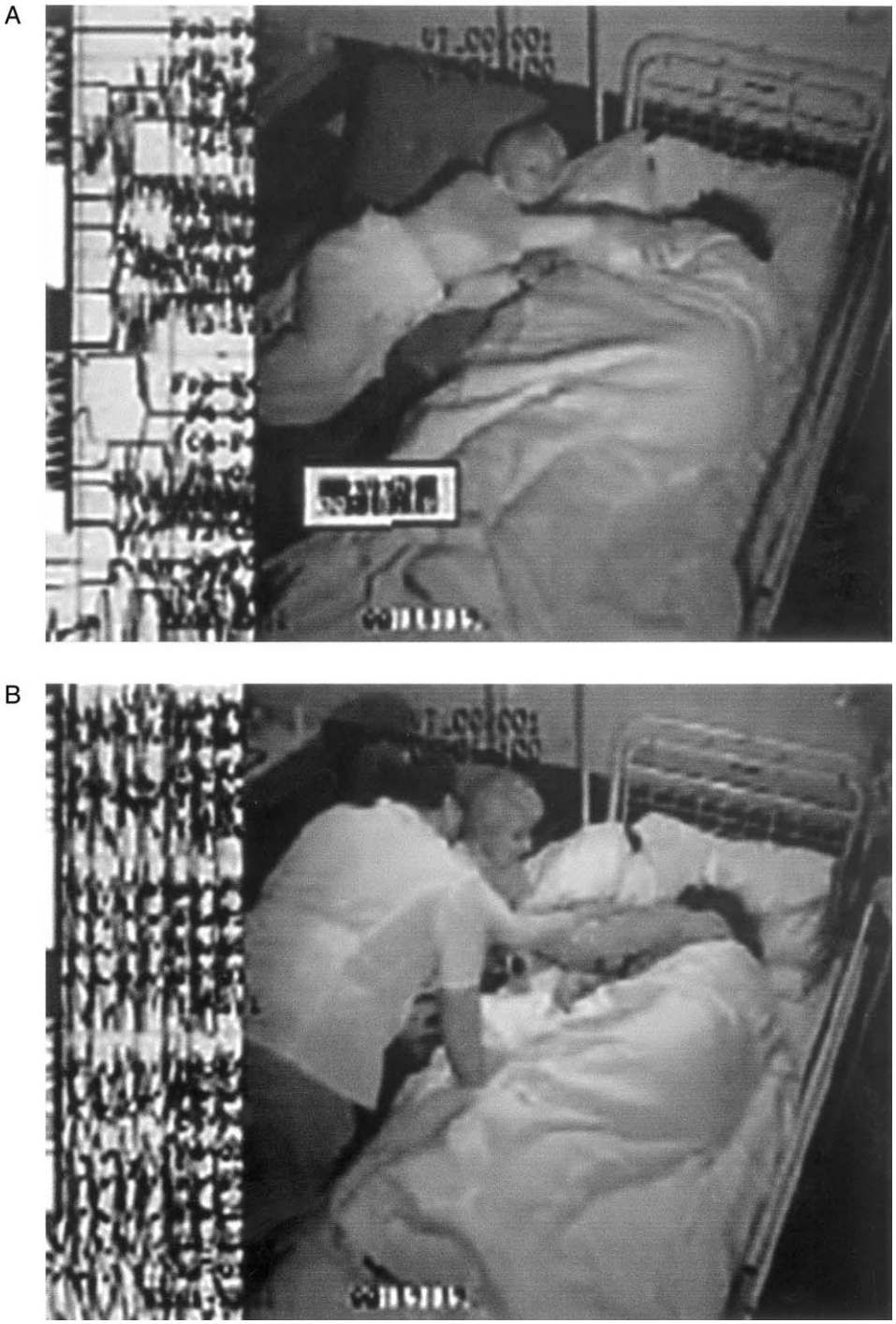

Fig. 5. (A) She is sleeping, when she suddenly stiffens with posturing of her left upper limb, here restrained by her mother (the right upper limb is obscured). Intense muscle activity is seen on the EEG trace. She cries out and at the same time jerking of the lower limbs begins. (B) One minute later rhythmic jerking continues, with now 2/econd generalised spike and wave maximum in fronto-central regions.

transversion in the *RSK2* gene, creating a suppression of the splicing site between intron 12 and exon 13.

Although it seems unlikely that the movement disorders seen in CLS patients will be attributable to specific mutations, we intend to undertake a collaborative study involving the large database of the Coffin–Lowry Syndrome Foundation to refine the semiology and to examine clinico-genetic correlations. Although CLS with paroxysmal events is relatively rare, its study may throw light on more common paroxysmal disorders.

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Table 2
Movement disorders and epileptic seizures in Case 2

Age at onset or age noticed (years)	Descriptions	Situation or stimulus	Contemporary diagnoses
6–7	Collapse, falling forward, folded legs 'like a shot cow'	Concentrating, distracted (sound startle not recognized)	Myoclonic epilepsy, clumsy
12	Dropped backwards onto occiput	N/K	Clumsy, psychological
16	Fall with stiffening	Sound startle	Epilepsy
29	Stiffening and shaking and incontinent	Nocturnal, from sleep, no stimulus	Epileptic seizure
30	Stiffening spasms, consciousness preserved	Nocturnal, from sleep, no stimulus	N/K
32	Collapse of neck and trunk	Her telling a joke	Cataplexy

N/K: not known.

Table 3
Patients with drop episodes and known age on the CLS Foundation database

Age group (years)	Drop episodes	Total (%)
<5	1	9 (11)
5– < 10	6	38 (16)
10– < 15	8	38 (21)
15– < 20	12	45 (27)
20 +	7	40 (18)
Total	34	170 (20)

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