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Coffin-Lowry Syndrome: A 20-Year Follow-Up and Review of Long-Term Outcomes

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The Coffin-Lowry syndrome has become well established since the first report of affected patients by Coffin et al. [1966: Am J Dis Child 112:205–213]. Since that time over a hundred cases have been reported and the responsible gene has been identified. However, there remains a paucity of long-term follow-up information on older patients with which to counsel affected families about prognosis. There is also much to be learned about genotype-phenotype correlations. In 1982 we reported 12 patients (including carrier mothers) from eight families, one of whom had died about the time the paper was written. Recently, we have been able to obtain follow-up information on six of the affected patients and one of the carrier mothers. A number of important complications have occurred, including premature death, loss of ambulation, and quadriplegia. This paper updates the medical histories of our patients and summarizes the clinically important complications that have been reported in patients with Coffin-Lowry syndrome. There are few data on patients over the age of 30, and much more longer term follow-up is required.

KEY WORDS: Coffin-Lowry; complications; mortality; aging; review

INTRODUCTION

Temtamy et al. [1975] were the first to recognize that the patients reported by Coffin et al. [1966] and by Lowry et al. [1971] had the same condition, and they coined the name Coffin-Lowry syndrome (CLS). Although, in the absence of a positive family history, the clinical diagnosis may be challenging in the young child [Wilson and Kelly, 1981; Hersh et al., 1984; Vles et al., 1984], the physical signs are usually distinctive and leave little doubt as to the diagnosis [Young, 1988]. The common major findings in males with this X-linked inherited syndrome include short stature; marked developmental disability; a somewhat thick or coarse face; downslanting palpebral fissures, often with hypertelorism or telecanthus; a broad nose with thick septum; prominent, everted lips; dental anomalies; and a characteristic hand with a doughy consistency and tapering fingers. A similar type of hand may also be seen in Börjeson-Forssman-Lehmann syndrome [Börjeson et al., 1962]. Musculoskeletal signs include pectus carinatum/excavatum, pes planus, and kyphoscoliosis, which may become severe. Radiographic changes include cranial hyperostosis, abnormal shape and end plates of the vertebral bodies, delayed bone age, metacarpal pseudoepiphyses, and tufting of the distal phalanges [Hunter et al., 1982; Gilgenkrantz et al., 1988; Young, 1988]. Expression in female gene carriers ranges from normal cognition, with or without minimal physical signs, to severity equaling that in the male.

Some of the early papers on CLS raised the question as to whether it might involve progressive decline in intellect [Coffin et al., 1966; Procopis and Turner, 1972; Temtamy et al., 1975]. However, little long-term follow-up information could be brought to bear on this question, although it did become accepted that the skeletal problems progressed with age [Hunter et al., 1982]. The possibility that CLS might be a disorder of chondrocytes, elastic tissue, or a storage disorder was also raised [Coffin et al., 1966; Temtamy et al., 1975; Gorlin et al., 1978], but could not be confirmed by others [Hunter et al., 1982]. However, reports suggesting a possible metabolic basis for the disease continued to appear [Beck et al., 1983; Miyazaki et al., 1989; Ishida et al., 1992]. Early linkage studies placed the CLS locus at Xp21-pter [Partington et al., 1988]. Subsequent refinement of the position and a candidate gene approach led to the identification of *RSK-2 (RP56KA3)* as the CLS gene [Trivier et al., 1996]. Knowledge of the gene has allowed the identification of males who are more mildly affected with CLS [Manouvrier-Hanu et al., 1999], although many questions remain about possible genotype-phenotype correlations [Jacquot et al., 1998].

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Notwithstanding that CLS is now widely recognized and reported, and that the causative gene has been isolated, there are few data that address the long-term outcome of affected patients. Most males with CLS have been reported at a relatively young age, and reports of later follow-up are rare [Machin et al., 1987; Partington et al., 1988; Fryns and Smeets, 1998]. In 1982 we reported 12 patients from eight families [Hunter et al., 1982]. A recent chance recontact by one of our families and significant complications in another of the patients that we had followed led to an attempt to follow up the patients we had described. This paper reports on the information obtained some 20 years after the original report and reviews the literature with an eye to identifying the types of long-term problems that may occur in CLS.

Updates of Patient Histories

H.B. was the propositus from family I in the report by Hunter et al. [1982]. It has not been possible to recontact this family, but some information was available from the hospital chart. When H.B. was 25 years old he was noted to have mega-trachea, "which may have been present from birth." At 26 years of age he was noted to have severe hearing loss with a significant air-bone gap. He would now be 35 years old, but he died; it has not been possible to determine when or why.

T.B. (family I, III-9) was the younger brother of H.B. There was an 8-year gap in the medical record from the time he was first reported until the age of 14 years. At that time he was profoundly retarded, nonverbal, and generally uncooperative. He was incontinent and remained so. He developed seizures, and at the age of 18 years these were poorly controlled by Tegretol®, Valproate®, and Haldol®. He was placed on nitrazepam because of a poor sleep pattern and lorazepam for his agitation. There was a period of good seizure control, but they recurred, possibly related to the mother's inability to maintain the proper medication routine. His behavior deteriorated, with an increasingly abnormal sleep pattern, nighttime agitation, emotional lability, and irritability. He was rarely violent. He was placed on Thorazine®. He was evaluated in psychiatry at the age of 20 years, and note was made that the mother was a poor historian but that it appeared there had been no acute behavioral changes. He tended to whine, pick things up, and walk around. He did use an occasional word. There was poor compliance with psychiatric follow-up and difficulty in balancing the behavioral and seizure medications.

Other medical problems have included chronic otitis media, which resulted in a right-sided mastoidectomy at the age of 15 years, followed by a similar procedure on the left a year later. He continued to be followed for hearing loss, but would not tolerate a hearing aid. At the age of 24 years he had a tracheostomy because of sleep apnea, but tended to remove the tube. A year later a radiographic study showed significant problems with swallowing and the presence of aspiration. His last outpatient visit was 2 years ago at the age of 29 years.

There was no follow-up information on the affected mother and sister who were reported originally [Hunter et al., 1982].

K.N. (family III, III-1; Hunter et al., 1982) was 5 years old when first reported. During childhood he was hyperactive, never developed good balance, and wore a helmet as protection from falls. He was dry during the day by the age of 10 years, but never developed nighttime bladder control. The mother identified an association between the full moon and poorer sleep and bladder control and an increase in hyperactivity. His intellectual development has been profoundly delayed. He developed single words in midchildhood and began small phrases at the age of 10 years. Now, at the age of 27 years, he is capable of expressing wants such as "to the room," "I'm hungry," and "go to bed." There has been no evidence of a decline in intellectual ability.

K.N. has had a number of significant health problems. At the age of 9 years he dislocated his left elbow. At the age of 12 years, during early puberty, he was diagnosed with asthma and a seizure disorder. The former was eventually well controlled with Becloforte® and Ventolin®, and the latter with Depakane®. At the same age he had onset of what, in retrospect, appear to have been the "drop-attacks" that have been reported in Coffin-Lowry syndrome. He would suddenly appear to be forced forward and would fall without any attempt at self-protection. There was no loss of consciousness, and he would recover quickly, although his mother thought he was weaker for a while afterward. These episodes occurred anywhere from twice a day to once a month, more often when he was agitated, and they have not recurred since a recent stroke.

At the age of 15 years he began to have difficulty with his balance and would lean against his parents for support. He was diagnosed as having lumbosacral disc disease and had surgery a year later that left him unimproved and with a foot drop that has required bracing since. At that time he was 153 cm tall ($<$ 3rd centile). About 3 years later he developed hypothyroidism that has been treated with Synthroid®. While there has been no evidence of hyperthyroidism, he has developed progressive exophthalmos and ectropion of the lower lids since about the age of 20 years.

At the age of 20 years he presented a fairly acute quadraparesis. Magnetic resonance imaging (MRI) showed a normal craniocervical junction and a narrow spinal canal of 8 mm in diameter. This was interpreted as congenital, as there were no osteophytes or disc herniation. The cord was compressed from C4–C6 with evidence of myelomalacia. There was evidence of thickening of the dura and of the ligamenta flava, compatible with calcification, in the lower cervical and upper thoracic spine. However, it was not thought that this was contributing to the stenosis. There was evidence of chronic degenerative disc disease and thickening of the ligamenta flava causing a moderate central stenosis in the lumbosacral spine, and there was a 20° gibbous at L2. He was admitted for an MRI under anesthesia and underwent a cervical decompression. There was some initial improvement, and he again became ambulatory, but within a year became increasingly symptomatic and

required assistance to walk. He underwent a cervical fusion; however, there has been no true progression and he has been essentially confined to a wheelchair since that time. Four years later he presented with a 4-month history of spiking temperatures to 39 or 40°C, and bone scans provided evidence of a septic focus in the right sacral wing. He became asymptomatic after 1-month intravenous and 1-month oral antibiotic therapy. Radiographs confirmed degenerative changes and a moderate kyphoscoliosis.

Recently, at the age of 26 years, he presented with difficulty maintaining an upright seated position and was difficult to help from the car. The next day the mother noted weakness of his right arm. A computed tomography (CT) scan showed evidence of a cerebrovascular accident above the head of the left caudate nucleus. Echography of his major vessels has been normal, and the etiology is not known.

When examined at the age of 27 years, he was overweight and confined to a wheelchair. His OFC was 56.8 cm (>50th centile); sitting height, 77.5 cm; and inner and outer canthal distances, 3.9 and 9.7 cm, respectively (both >97th centile). An accurate height could not be obtained. He had the characteristic facial appearance of the syndrome (Fig. 1a), with the addition of prominent eyes and inflamed eyelids. His teeth were small, well spaced, maloccluded, and malaligned. His chest showed the typical pectus carinatum and distortion secondary to the kyphoscoliosis. The characteristic changes of his hands were more marked than when he was younger (Fig. 1b) and were 17.3 cm long, with a middle finger length of 7.1 cm.

C.N., the mother of K.N., was reported as showing mild physical signs in 1982 [Hunter et al., 1982]. She has enjoyed good health and has had no complications since 1982.

M.B. was individual III-7 from family II [Hunter et al., 1982]. At that time he was 5 years old, was developing simple speech, and showed a relatively mild facial appearance of CLS. He had been diagnosed as having severe sensorineural hearing loss. Radiographs of the spine were normal. Since that time M.B. has enjoyed general good health, although there have been some problems that have been difficult to clarify.

He has been followed by orthopedics for about the last 10 years, primarily because of his joint laxity, and at the age of 14 or 15 years he began to have some difficulty walking because of what appears to have been Osgood-Schlatter disease. He recovered, but presented with weakness at the left knee 8 years later. There were no objective findings, and he responded to physiotherapy. When he was 25 years old, the parents noted that he hesitated when rising from the sitting position, and they became convinced he had back pain. Spinal radiographs showed a slight midthoracic scoliosis, some degenerative osteophytes at several levels, a decrease in the L5–S1 space, and some arthrosis of facets at L4–S1. An MRI of the lumbosacral spine showed a grade I/IV spondylolisthesis and a narrowing of the canal to 9 mm at L5–S1. The parents considered that M.B. responded to anti-inflammatory and physiotherapy treatment. He still has difficulty rising from the sitting position, but he is severely overweight and has poor coordination. M.B. has had two episodes of "fainting." One occurred at night, when he rose and fell. The father found him cold and pale, but he recovered quickly. The second occurred

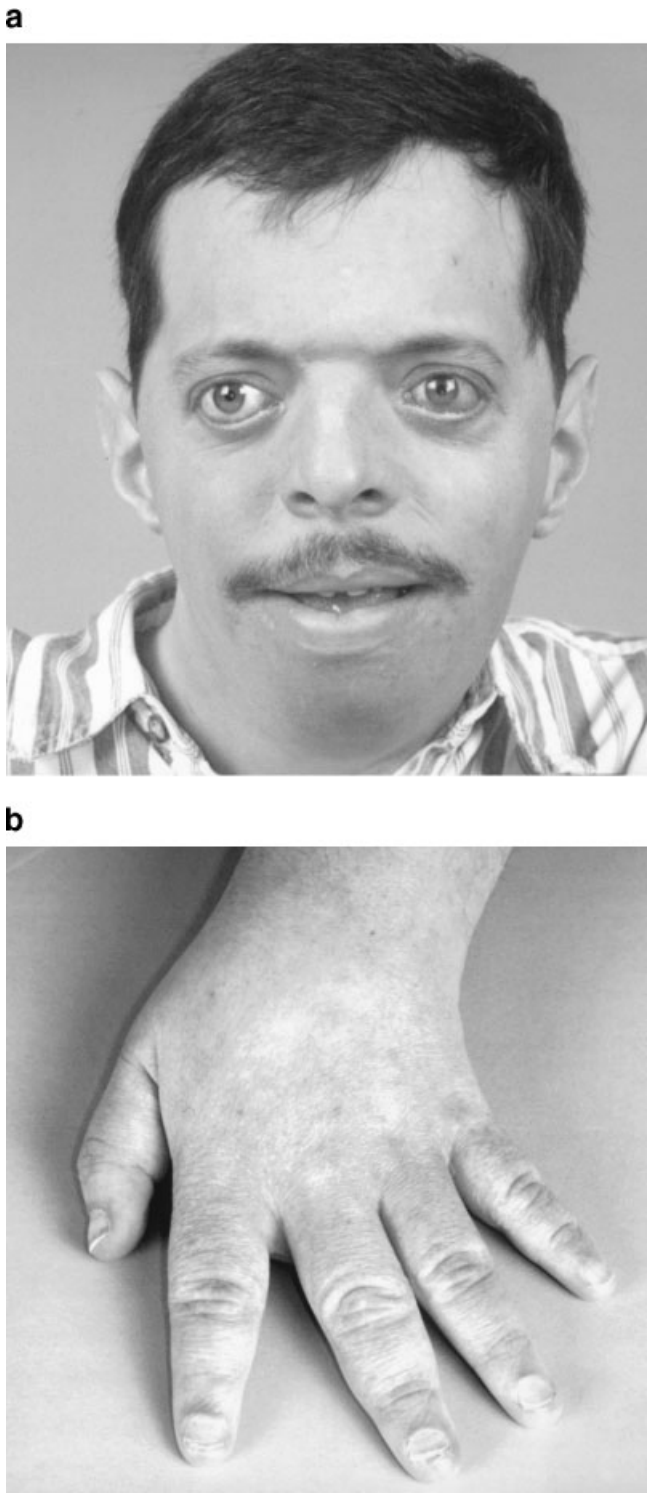

Fig. 1. **a:** Face of K.N. showing downslanting palpebrae, slight ectropion with inflamed lids, prominent eyes, full lips, a small jaw, short nose, and large ears. **b:** Hands of K.N. showing full, fleshy, tapering characteristics.

on coming inside after a fall on an ice rink. It was reported that he fell backwards and became pale, the whole episode lasting a few seconds.

M.B. continues to live with his parents and spends the day in an atelier, where he helps with simple tasks such as cleaning tables and washing dishes. His behavior has been happy and easygoing, with his favorite pastimes being puzzles and listening to music. There appeared to be a period of adolescent adjustment when he was disaffected and would not participate in school or in self-care. Later, at the age of 23 years, there was a move to a new situation, with more noise and people, and he became aggressive. However, this soon resolved.

At the time of this assessment M.B. was 26 years old. He had a vocabulary of several hundred words and communicated in rapid, short (three- or four-word) phrases, although in no way could one carry on a conversation. He could follow instructions, if given in simple statements, with two and sometimes three objectives. He was 170 cm tall (25th centile), had an OFC of 56.2 (>50th centile), and weighed 91.8 kg (97th centile). His span was less than his height (168.5 cm), suggesting somewhat short limbs; an accurate lower segment measurement could not be obtained. His obesity was central, and the limbs showed poor muscle bulk. His craniofacial appearance had coarsened with age (Fig. 2a). His ears were large (7.1 cm). Of particular note, he no longer used hearing aids and appeared to have normal hearing. There was no telecanthus or hypertelorism (inner canthal distance, 3.1 cm; outer, 7.8 cm); the palpebrae were downslanting. He had lost a number of teeth to trauma and poor hygiene, and the remaining lower incisors were small and widely spaced. The palate was narrow with prominent palatal shelves, and the mandible was small. His pectus excavatum was no longer present; he had a thoracic kyphosis, but no visible scoliosis. All major and minor joints were hyperextensible, and the hands were more characteristic of CLS than they had been at the age of 5 years (Fig. 2b).

M.D. (family IV, II-1) (Hunter et al., 1982) was 26 years old when first reported. He lived in an institution for persons with mental retardation until he was 42, at which time he entered a group home nearer his family. At the time of his most recent evaluation he was 46 years old, and the staff at the home reported that his mother and sister appeared to have features of the syndrome. When he joined the home he was able to walk, but over the ensuing 4 years he became almost entirely confined to a wheelchair. He had drop-attacks where he would fall to the floor and then laugh. These could occur spontaneously, but were usually triggered by a tactile or auditory startle response. It was stated that he had become unsteady and unable to support himself, but that he was able to walk a short distance with the assistance of two staff members. His last four teeth had been removed recently because of caries, and although he has a good appetite, his food is largely soft or pureed. He can use a cup and spoon. There was a history of eye infections, particularly of the right, which cleared with eyedrops. His vocalizations are limited to sounds, often a "caw" sound that is used to express displeasure. He has a preference for specific staff and will seek their attention, and he can assist with dressing. He is time-toileted during the day and diapered at night. His sleep pattern is sometimes disturbed, and he is not capable of turning from side to side in bed or of turning his head while sitting. There has been a gradual loss of interest

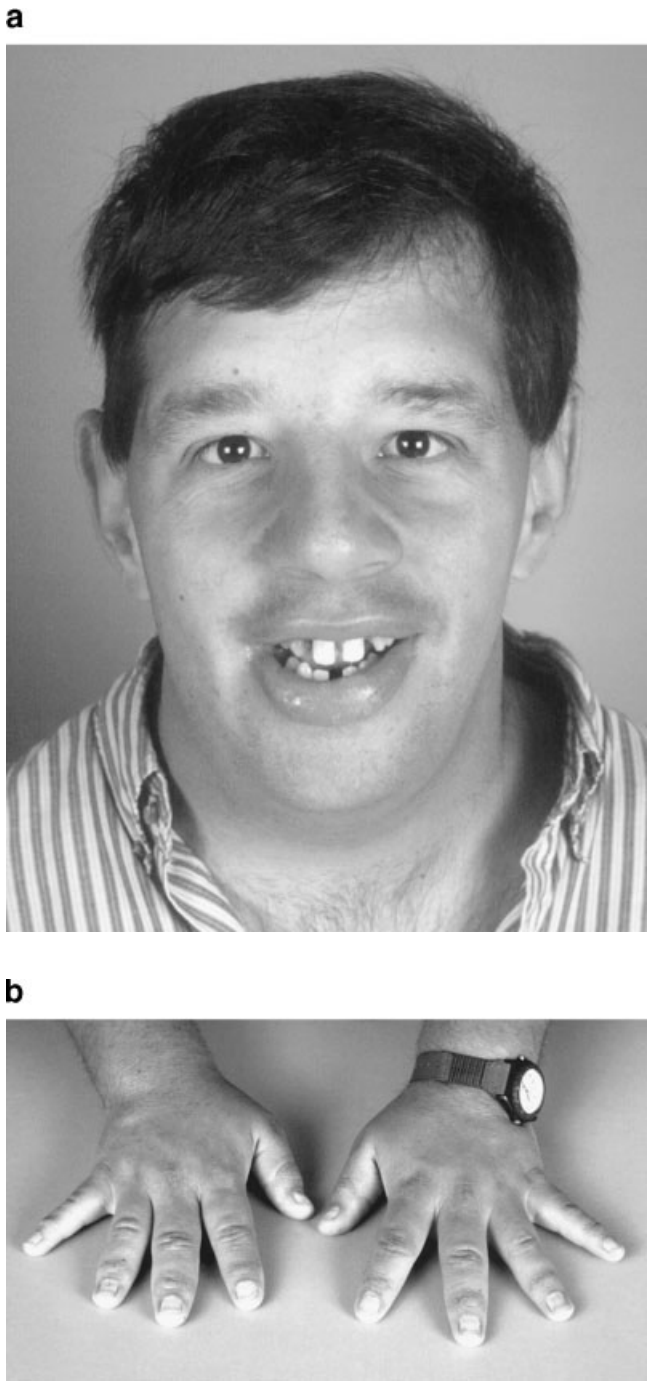

Fig. 2. **a:** Face of M.B. continuing to show mild facial signs with large ears, prominent brows, minimally downslanting palpebrae, full everted lips, and small, spaced teeth. **b:** Hands of M.B. showing characteristic hands that are more apparent than when he was young.

in activities such as television and games, although a psychiatrist has judged that he is not psychotic or depressed.

On examination he showed the characteristic facial appearance of CLS (Fig. 3) and had an OFC of 57cm. He was cooperative but nonverbal, and responded by smiling or "cawing." His inner canthal distance was 4 cm and his outer 10 cm (both >97th centile), and his ears measured 6.5 cm (>97th centile). In addition, his nose had a "fractured" look, he would not move his head from side to side, and there was limitation of full extension at the elbows and of pronation and supination. He could not bend forward; there was a significant pectus carinatum, but no significant scoliosis. His hand measured 18 cm, and his middle finger was 6.8 cm in length. There were no cardio-respiratory signs, although his heart sounds were poorly heard and he had chronic pitting edema of his lower legs and forearms. A cardiac evaluation was recommended. His strength was thought to be decreased; deep tendon reflexes were normal, except they could not be elicited at the ankles.

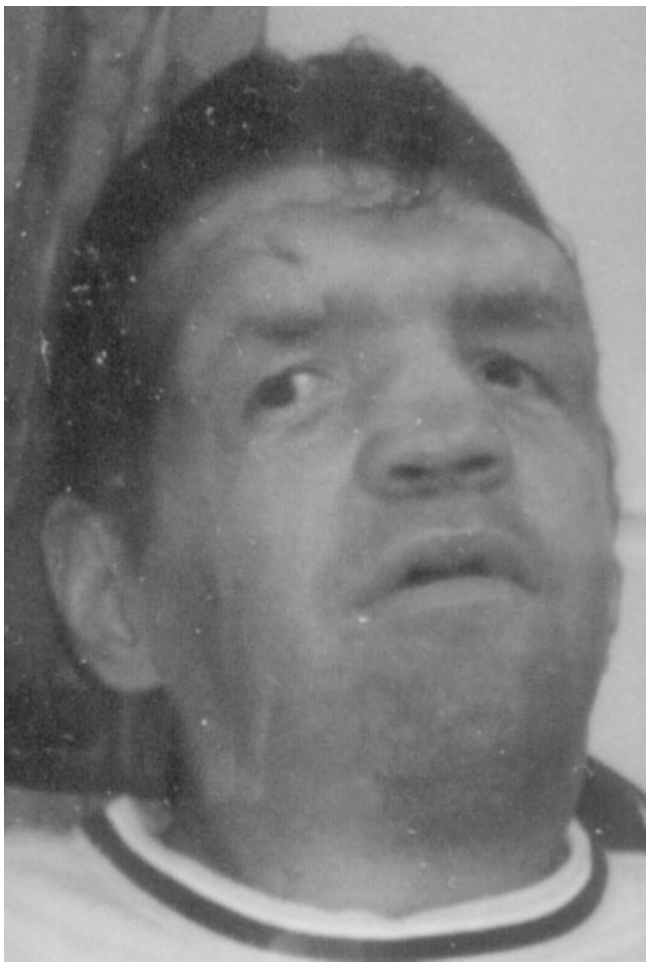

Fig. 3. Face of M.D. illustrating marked downslanting palpebrae with hypertelorism, a pugilistic nose, full lips, and edentulous mouth.

E.E. was individual II-3 from family VI [Hunter et al., 1982]. She has been in institutionalized care since the age of 11 years and has had no contact from her family. Medical documentation from 1982, when she was 24 years old, until the present is sparse. At the age of 33 years, her IQ was assessed as <20 using the Stanford-Binet, and she was noted to have minimal and inconsistent communication, although she would carry out a number of activities of daily living after verbal prompting. More recent assessments have suggested a somewhat higher level of functioning. She is capable of selecting a preferred set of clothes and partially dressing herself. She is actively involved in several recreational activities and is capable of finding her way to activities on her own. Generally quiet, she will interact with familiar staff, especially in a one-on-one situation, and does continue to learn new skills. With guidance she will make her bed, set a table, and help with cleaning. She is generally dry during the day, but not at night, and may wet or soil at times of stress. Dramatic changes in mood and behavior may occur without apparent triggers, but generally her behavior is not difficult. Language is limited to single words and occasional brief sentences such as "I did it myself" or "go outside." She will generally follow instructions, which can contain up to two objectives, from familiar staff.

When examined at the age of 45 years, it was reported that she had frequent urinary tract infections, but these were not culture proven. She had a history of gut sensitivity to tomato-based products and irritable bowel syndrome, which was treated with Dicetel®. Otherwise, she had enjoyed good health. She was 156 cm tall (25th centile) with a reduced span of ~145 cm. Her OFC was 54.3 cm (40th centile). Her facial features were relatively mild and characterized by a very low nasal bridge, which appeared less developed than in her earlier photographs, and wide-spaced eyes with downslanting fissures (Fig. 4). Ocular measurements could not be obtained. Both eyes were tested at −9.00, −4.00 axis 180. The fundus could not be examined. E.E. had a chronic complaint of red running eyes, and the lower lids showed a mild ectropion. Her eyes were mildly more prominent than average. The teeth were well spaced with a marked diastema. The four third molars were absent, and the upper right bicuspid was rotated 90° and was two-thirds normal size. Her mild kyphoscoliosis had not increased, and the hands remained typical of CLS (Fig. 4).

J.S. (family V, II-4) had died of cardiovascular complications just before the original publication, and no new information could be gleaned from her chart. No follow-up was obtained on R.G. and J.M., who were described in the original report.

DISCUSSION

The main impetus for the current study was to provide information about the long-term prognosis in CLS. In addition to updating the history on several of our patients, the literature was reviewed for complications in previously reported cases [Coffin et al., 1966; Martinelli and Campailla, 1969; Lowry et al., 1971; Procopis and Turner, 1972; Jammes et al., 1973;

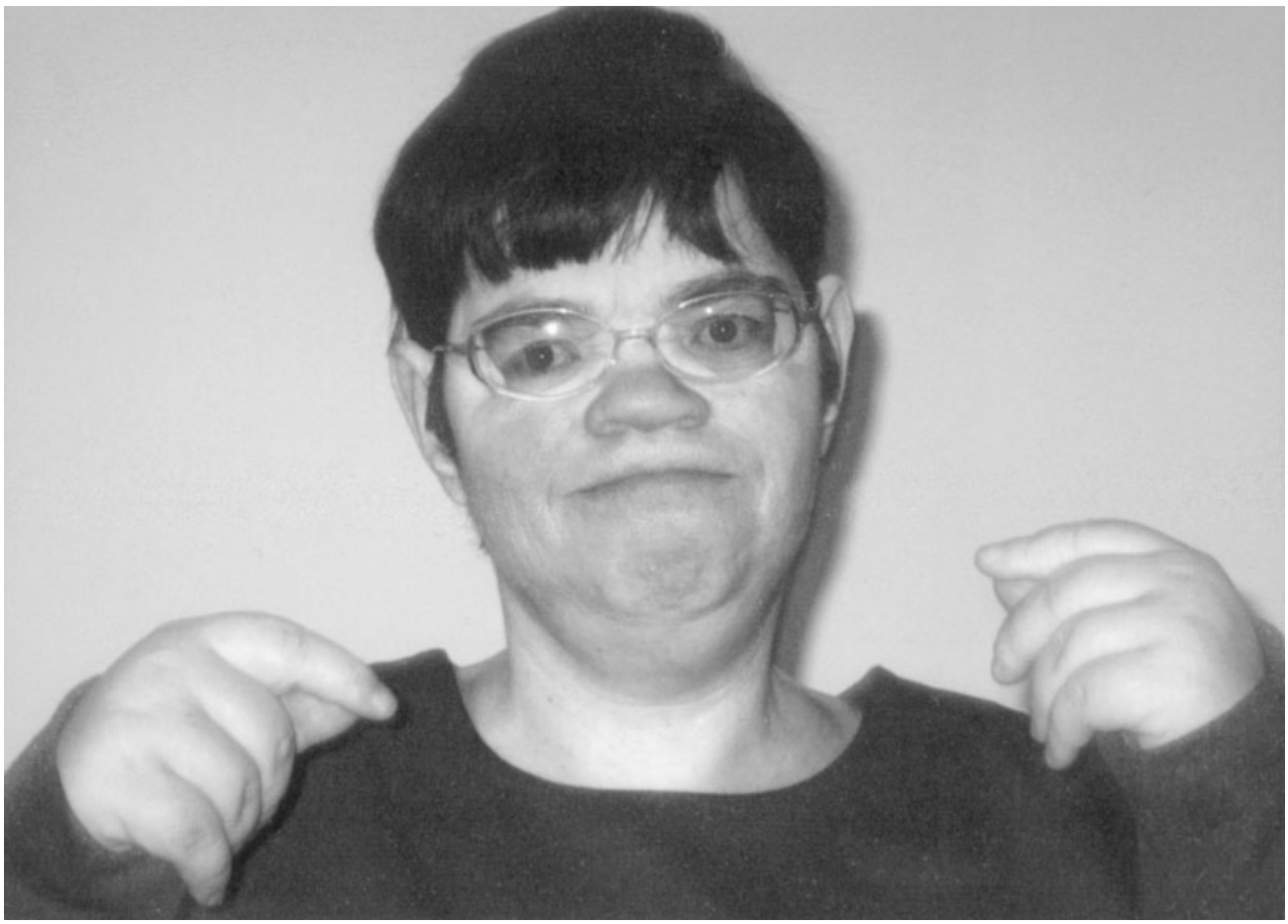

Fig. 4. Face and hands of E.E. showing minimal palpebral downslant with eyelid inflamation, a pugilistic nose with a low bridge, large ears, and full fleshy, tapered fingers.

De Marco, 1975; Temtamy et al., 1975; Merchant, 1976; Sylvester et al., 1976; Fryns et al., 1977; Wilson and Kelly, 1981; Hunter et al., 1982; Kousseff, 1982; Haspeslagh et al., 1984; Hersh et al., 1984; Vles et al., 1984; Christodorescu, 1987; Collacott et al., 1987; Della Cella et al., 1987; Machin et al., 1987; Charles et al., 1988; Gilgenkrantz et al., 1988; Krajewska-Walasek et al., 1988; Partington et al., 1988; Miyazaki et al., 1989; Padley et al., 1990; Ishida et al., 1992; Hartsfield et al., 1993; Lacombe et al., 1993; Higashi and Matsuki, 1994; Özden et al., 1994; Sivagamasundari et al., 1994; Soekarman and Fryns, 1994; MacDermot et al., 1995; Plomp et al., 1995; Crow et al., 1998; Fryns and Smeets, 1998; Kondoh et al., 1998; Nakamura et al., 1998; Rosanowski et al., 1998; Manouvrier-Hanu et al., 1999; Caraballo et al., 2000; Day et al., 2000]. Patients reported in abstract form by Casey et al. [1978] and Vine et al. [1986] were not included, nor was the patient reported by MacDermot et al. [1995], who Fryns [1996] considered to have CLS. A copy of the report by Capotorti et al. [1985] could not be obtained. Finally, Temtamy et al. [1975] reported their patients as a group, and so not all the age-related data were separable. A total of 111 patients (89 male and 22 female), as well as 38 obligate carrier mothers and 8 "affected" sisters who were mentioned en passant, were included. The age of the patients when they were last reported is summarized in Figure 5. This shows that a relatively small number have been followed beyond their twenties.

The characteristic craniofacial, appendicular, and radiological signs of CLS have been well described [Hunter et al., 1982; Gilgenkrantz et al., 1988; Young,

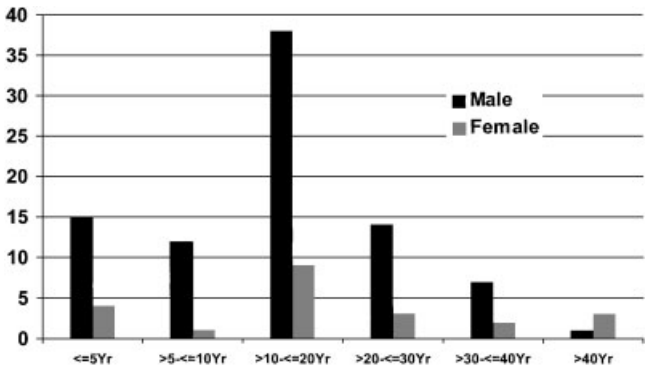

Fig. 5. A summary of the ages when male and female patients with CLS were last reported.

1988], and it was not intended to include them in this review. However, it was very evident from this review that, as has been stated before [Wilson and Kelly, 1981; Hersh et al., 1984; Vles et al., 1984], the CLS gestalt does become more evident with age. This would appear to be the result of the normal age-related effect of craniofacial development, rather than a true progressive deterioration or coarsening. It is also clear that, when present, a kyphoscoliosis may be progressive and become a significant cause of morbidity and probably also mortality (vide infra). The major age-related changes are discussed below and are summarized in Table I.

Mortality

Thirteen patients had died by the time of their initial description or at the time of follow-up (12 male, 13.5%; 1 female, 4.5%) [Jammes et al., 1973; Hunter et al., 1982; Machin et al., 1987; Gilgenkrantz et al., 1988; Krajewska-Walasek et al., 1988; Partington et al., 1988; Sivagamasundari et al., 1994; Fryns and Smeets, 1998; this report (H.B.)]. (The patient reported by Charles et al. [1988] is included in the series by Gilgenkrantz et al. [1988].) The mean known age at death in the males was 20.5 years (range, 13–34), and the woman died at age 48 years [Hunter et al., 1982]. Cardiovascular anomalies appeared to play some role in six cases, although there were often concurrent problems, such as panacinar emphysema [Machin et al., 1987]. Other respiratory complications occurred in four cases [Partington et al., 1988; Fryns and Smeets, 1998], and one patient aspirated following a seizure [Gilgenkrantz et al., 1988]. The progressive kyphoscoliosis may be a contributing factor to cardio-respiratory compromise [Ishida et al., 1992; Fryns and Smeets, 1998]. In two cases the cause of death was unknown [Krajewska-Walasek et al., 1988; this report (H.B.)]. One patient died of Hodgkins disease [Sivagamasundari et al., 1994], and it is of note that one obligate carrier mother (1/38) also died of that disease [Gilgenkrantz et al., 1988]. A monozygotic twin of another patient died of a posterior fossa tumor when 40 days old [Hartsfield et al., 1993], and another mother with physical signs of CLS had a Wilms tumor [Manouvrier-Hanu et al., 1999]. Affected sibs who had died but were not described have been reported by Coffin et al. [1966], Caraballo et al. [2000], and Partington et al. [1988].

Cardiovascular

Thirteen patients (12 male, 13.5%; 1 female, 4.5%) were reported to have a cardiovascular malformation [Jammes et al., 1973; Temtamy et al., 1975; Hunter et al., 1982; Della Cella et al., 1987; Machin et al., 1987; Gilgenkrantz et al., 1988; Krajewska-Walasek et al., 1988; Ishida et al., 1992; Plomp et al., 1995; Massin et al., 1999]. The actual rate may be significantly higher, as many patients have not had a thorough cardiovascular examination, including an echocardiogram. Seven patients (one female) had an incompetent and/or prolapsed mitral valve, and in three this appeared to contribute to premature death. In two cases this was known to be associated with abnormally short chordae [Machin et al., 1987; Massin et al., 1999]. Other abnormalities included a cardiomyopathy in three patients, one of whom had endocardial fibroelastosis [Gilgenkrantz et al., 1988; Massin et al., 1999], tricuspid changes in two cases [Machin et al., 1987], and one case each of abnormal aortic valve with aortic root dilation [Della Cella et al., 1987] and pulmonary dilatation [Machin et al., 1987]. Two patients had congestive heart failure of unspecified cause [Jammes et al., 1973; Ishida et al., 1992].

Neurological Signs

Significant mental retardation is a hallmark of the hemizygous male with CLS. The distribution of severity of mental retardation by age at reporting is summarized in Figure 6. In abstracting the data from the literature it was assumed that the terms profound, severe, and moderate were being used correctly. However, even if they were not, there is no reason to assume a systematic bias that would affect the age distribution. The data suggest that early assessments of developmental potential may be overly optimistic. While seizures are commonly reported, they probably are not more frequent

TABLE I. Summary of Age Related Problems and Changes in Coffin-Lowry Syndrome

Craniofacial	Changes are probably normal age related maturation. Facial signs are more apparent with age; primarily fullness of the brows and the lips.
Dental	Late eruption and premature loss. Hypodontia, abnormal tooth shape and position.
Hearing	Increased sensorineural (may be late onset) and probably conductive hearing loss.
Vision	Cataract and retinal changes reported in a few patients; possibly underascertained.
Cardio-respiratory	Cardiomyopathy, valvular and other structural cardiac abnormalities; may be underascertained. Increased rate pneumonia and cardiorespiratory compromise due to kyphoscoliosis. Panacinar emphysema reported at autopsy.
Neurological	Most males are severely to profoundly retarded; early assessments may overestimate potential. Venticulomegaly is not usually symptomatic or progressive. Characteristic “drop attacks”; onset mid-childhood to teens. Progressive changes in reflexes, loss of strength, loss of mobility, onset of apnea; may be due to cervical/lumbar spinal stenosis+/−kyphoscoliosis.
Psychiatric	Possibly increased rate of psychiatric disease, especially in female gene carriers.
Musculoskeletal	Common mid-childhood or later onset of kyphoscoliosis; often progressive. Calcification of the ligamenta flava; may cause spinal stenosis.
Gastrointestinal	Single case reports; jejunal or colonic diverticuli, pyloric stenosis, rectal prolapse.
Mortality	Increased rate premature death; cardiac, respiratory, neurological, and kyphoscoliosis related causes.

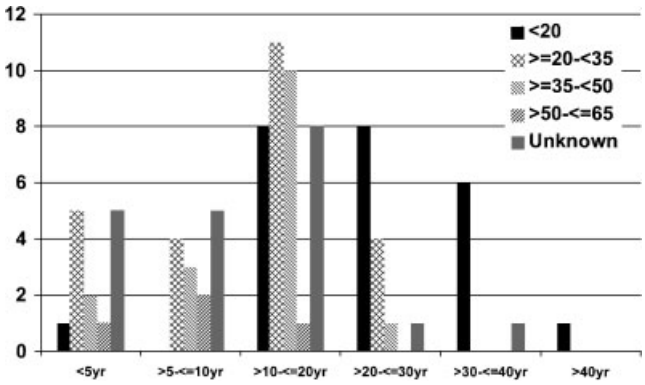

Fig. 6. A summary of the degree of mental retardation by IQ, at the time they were reported, of the male patients with CLS.

than expected in a population with severe to profound retardation. Most neuroimaging studies either are normal or show nonspecific increased ventricular and/or subarachnoid space, although abnormalities of the corpus callosum have been observed [Soekarman and Fryns, 1994; Özden et al., 1994; Kondoh et al., 1998]. Kondoh et al. [1998] reported multiple, focal, frontal, and parasagittal hypodensities on the MRI scan of an affected 6-year-old boy, but there have been no subsequent reports of these findings, whose specific nature remains obscure.

The severe intellectual impairment of most patients generally precludes a complete neurologic evaluation and may lead to delays in the recognition of severe complications, such as those described for K.N. in this report. A loss of muscle strength and mass, particularly affecting the legs, has been noted in several reports [Procopis and Turner, 1972; Hartsfield et al., 1993; Crow et al., 1998], as both have increased [Jammes et al., 1973; Temtamy et al., 1975; Hersh et al., 1984; Gilgenkrantz et al., 1988; Ishida et al., 1992] and decreased [Jammes et al., 1973; De Marco, 1975] deep tendon reflexes. Foot drop [Temtamy et al., 1975], loss of the ability to walk [Procopis and Turner, 1972; this report (K.N. and M.D.)], and a developing paraplegia have also been reported [Machin et al., 1987; this report (K.N.)]. Vine et al. [1986] reported a 22-year-old male with a normal electromyogram and muscle biopsy, but with decreased amplitude and latency on nerve conduction studies. Neurogenic changes on biopsy were reported by Temtamy et al. [1975]. Ishida et al. [1992] reported three patients in their twenties with progressive spasticity, which they attributed to spinal stenosis associated with calcification of the ligamenta flava. Our patient (K.N.) also had evidence of cervical and lumbar spinal stenosis and thickening with calcification of the ligamenta flava. Sleep apnea requiring a tracheostomy [this report (T.B.)], stroke [this report (K.N.)], and congenital narrowness of the cervical canal [this report (K.N.)] do not appear to have been reported before in CLS.

Drop-Attacks

It appears that Padley et al. [1990] were the first to recognize a now well-established, characteristic, and possibly unique neurological phenomenon in CLS. They described a male patient who, at the age of 5 years, began to experience episodes of falling backwards, from which he would recover immediately. The condition was further described and its neurophysiology elucidated by Nakamura et al. [1998] and Crow et al. [1998]. The episodes may have onset from midchildhood to the teens, both males and females have been affected, and they are triggered by unexpected tactile or auditory stimulus or by excitement. The episodes may become so frequent as to require a wheelchair for protection [Crow et al., 1998].

Electrophysiologically it has been shown that the electroencephalogram remains unchanged, while the electromygram of the lower limbs becomes silent for a period of about 60–80 msec after the stimulus [Crow et al., 1998; Caraballo et al., 2000]. These episodes appear to most closely resemble cataplexy, but appear to be distinct from that condition, as well as from hyperekplexia and negative myoclonus [Crow et al., 1998; Caraballo et al., 2000]. Fryns and Smeets [1998] made a retrospective diagnosis of these drop-attacks in two patients they had earlier reported as having seizures, and they reported a third affected patient whose signs disappeared after corrective surgery for kyphoscoliosis. However, not all patients with drop-attacks have had severe kyphoscoliosis (e.g., M.D. [this report]). Our patients K.N. and M.D. appear to have experienced this phenomenon, but now they are essentially confined to a wheelchair. It is unclear whether the two episodes experienced by M.B. are related to this phenomenon. The patient reported by Ishida et al. [1992] as having "occasional loss of consciousness" and by Plomp et al. [1995] as having "seizure-like episodes" may have been similarly affected. The true prevalence of drop-attacks in CLS is not known, but 3 of 22 patients known to Fryns and Smeets [1998] and at least two in our series were affected.

Psychiatric Changes

One male [Gilgenkrantz et al., 1988] and three female patients [Collacott et al., 1987; Partington et al., 1988] have had signs suggestive of, or diagnostic of, having a psychosis, and the description of some of the behavior of one of our patients is suspicious (T.B.). Furthermore, an obligate carrier mother with physical signs of CLS was a chronic schizophrenic [Jammes et al., 1973]; one sister of a patient, who herself had a coarse face, developed psychosis [Haspeslagh et al., 1984]; and the mother of four patients developed what sounded like a bipolar illness in her early twenties [Sivagamasundari et al., 1994]. These data, albeit preliminary, do suggest an excess of psychiatric illness among female gene carriers. Six (8.8%) of 22 female patients, 38 heterozygous mothers, and 8 "affected" sisters were affected.

Kyphoscoliosis

Information concerning the presence or absence of kyphoscoliosis is not always recorded in case reports, and there is no standard for its categorization into mild, moderate, and severe. Thus the true prevalence and

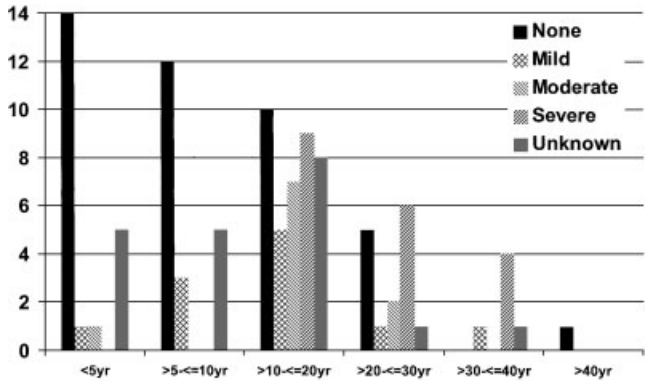

Fig. 7. The degree of kyphoscoliosis by age at the time of report of the male patients with CLS.

severity of kyphoscoliosis in CLS remains unclear. However, at least 41 males (47.1%) and 7 females (31.8%) have been affected by kyphoscoliosis; Figure 7 shows the reported severity against the age of the patient. From these data it does appear clear that kyphoscoliosis is uncommon in early childhood and becomes progressively more severe with age. However, a significant proportion of patients remain free of significant kyphoscoliosis. Cardio-respiratory compromise may result from severe kyphoscoliosis [Fryns and Smeets, 1998].

Ocular Abnormalities

Significant eye abnormalities do not appear particularly common in CLS. Two patients have been reported with cataract [Hunter et al., 1982; Plomp et al., 1995], one of whom had retinal ablation [Plomp et al., 1995]. Retinal pigment atrophy was reported in one patient by Coffin et al. [1966], and the patient of Caraballo et al. [2000] had bilateral optic atrophy. One of our patients (K.N.) developed an exophthalmos, and he and two of our other patients (M.D. and E.E.) have chronic eyelid irritation. E.E. is also a high myope.

Hearing Loss

At least 14 males and 1 female with CLS have been reported to have sensorineural or mixed hearing loss [Hunter et al., 1982; Collacott et al., 1987; Hartsfield et al., 1993; Higashi and Matsuki, 1994; Sivagamasundari et al., 1994; Rosanowski et al., 1998]. Two of our patients (T.B. and H.B.) appear to have suffered chronic conductive loss. It is not possible to estimate the rate of hearing loss in CLS from these data because not all patients have had formal hearing testing and because the purpose of several of these papers was to report the hearing loss, thus introducing a reporting bias [Hartsfield et al., 1993; Higashi and Matsuki, 1994; Sivagamasundari et al., 1994]. However, it does seem clear that hearing loss is not a chance occurrence in CLS, and a number of interesting features emerge. There may be a trend to clustering of the hearing loss within families, and its onset may occur later, after documented normal hearing earlier in childhood [Rosanowski et al., 1998]. A malformation of the labyrinth may be causative in some cases [Higashi and Matsuki, 1994]. Finally, the history of our patient M.B., who wore hearing aids for profound sensorineural hearing loss as a child and now hears perfectly without assistance, is puzzling.

Dental Problems

Abnormalities in dentition are extremely common and most likely underascertained in CLS. They include hypodontia [Temtamy et al., 1975; Gilgenkrantz et al., 1988; Plomp et al., 1995], small, abnormal-shaped or widely spaced teeth [Temtamy et al., 1975; Partington et al., 1988; Hartsfield et al., 1993; Soekarman and Fryns, 1994; Plomp et al., 1995; Manouvrier-Hanu et al., 1999], delayed eruption of the primary dentition [Sylvester et al., 1976; Hartsfield et al., 1993], malpositioning [Gilgenkrantz et al., 1988], and premature loss of teeth [Kousseff, 1982; Haspeslagh et al., 1984; Hartsfield et al., 1993; Day et al., 2000]. Day et al. [2000] attributed the premature dental loss to hypoplastic cementum with a paucity of peridontal membrane fibers.

Findings in Single Cases

Additional findings that have been reported only once to date include rectal prolapse [Coffin et al., 1966], uterine prolapse [Temtamy et al., 1975], multiple jejunal diverticuli [Machin et al., 1987], sigmoid colon diverticuli with reduced numbers of ganglion cells [Machin et al., 1987], pyloric stenosis [Gilgenkrantz et al., 1988], popliteal ganglion [Gilgenkrantz et al., 1988], unilateral renal agenesis [Plomp et al., 1995], anterior-placed anus [Manouvrier-Hanu et al., 1999], and increased facial pigmentation [Sylvester et al., 1976]. Finally, one of our patients (H.B.) was found to have an enlarged trachea, one suffered sleep apnea (T.B.), and one had a narrow cervical spine canal (K.N.).

CONCLUSIONS

Although it is 35 years since the original report of CLS, there remain very few data concerning patients over the age of 30 years. There is a need to report the health status of older patients, unbiased for selection of specific findings, in order to provide better preventive care for patients and advice to families and health-care workers. Premature death is a significant risk and occurred in at least 11% of cases (13.5% of males). The rate may be even higher given the frequent mention of affected sibs who were unreported because they had died. Cardiovascular complications are an important contributor to some of the premature deaths and affect at least 11% of patients. While mitral valve involvement appears most common, there may be other changes, including a cardiomyopathy. It is likely that cardiac involvement and several other complications, including neurological, psychiatric, auditory, and visual, are underascertained because many of the patients cannot communicate and they have not had complete evaluations. Factors that may contribute to the lack of evaluation and continued follow-up

are that a large proportion of patients (at least 35) have been institutionalized without contact with their families, and many of the families have mothers who are intellectually impaired and a dysfunctional dynamic.

It is clear from this review that patients with CLS require a periodic review of their cardiac, neurological, ocular, auditory, and dental status. The neurologic evaluation should look for evidence of spinal cord involvement at both upper and lower levels and for a history of drop-attacks, which may be mistaken for seizures. Prevention of progressive kyphoscoliosis, which may compromise mobility and cardio-respiratory status, should be a goal. Many patients, even in the absence of kyphoscoliosis, develop a stiff, bent forward gate. At this time it is unclear whether physiotherapy might prevent its occurrence. It should be kept in mind that there may be an excess of psychiatric illness, specifically among women with the CLS gene.

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