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A Comprehensive Description of the Severity Groups in Cockayne Syndrome

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Cockayne syndrome (CS) is a rare degenerative disorder with a common set of symptoms but a very wide variation in phenotype. The variation is sufficiently wide that CS patients have traditionally been described in three different severity groups. Unfortunately, there is no single source for information about the different severity groups. This problem can complicate not only diagnosis, but accurate prognosis as well. The goal of this study was to describe the phenotypic variation in CS as completely as possible. This article provides extensive descriptions of traits common to each group and their degree of severity in each group. Forty-five people with CS were surveyed and information from the published literature was used to increase the sample sizes for calculations. This study provides new information, including statistical data for each of the three severity groups (mean age at death, average head circumference, and average length or stature). The study includes cerebro-oculo-facial syndrome (COFS) as a severe form of CS, based on results of recently published genetic studies performed by other authors. This study proposes revised names for CS severity groups: severe, moderate, and mild. The groups were formerly called *Type II/early onset CS*, *Type I/classical CS*, and *Type III/atypical/mild/late-onset CS*, respectively. A fourth newly documented group, *UV sensitivity only/adult onset*, is also described. Average ages of death were calculated as 5.0 years (severe), 16.1 years (moderate), and 30.3 years (mild). © 2011 Wiley-Liss, Inc.

Key words: Cockayne syndrome; COFS; neurodegenerative diseases; photosensitivity disorders; hearing loss; sensorineural; developmental disabilities; *ERCC6*; *ERCC8*

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INTRODUCTION

Cockayne syndrome (CS) is a multi-system degenerative disorder. Major clinical manifestations include photosensitivity, microcephaly, dwarfism, a characteristic facial appearance, very low body weight in most patients, developmental delays, premature aging, musculoskeletal abnormalities (such as flexion contratures), tremors, progressive sensorineural deafness, visual problems including cataracts and salt-and-pepper retinopathy, severe crowding of permanent teeth, and CNS abnormalities (demyelination, brain atrophy, and calcifications). These features have been consistently documented in the literature, including the last major review of CS [Nance and Berry, 1992].

The extremities of CS patients (especially their feet) tend to be cold and/or bluish, and their hands/arms are often disproportionately large compared to the body as a whole [Cockayne, 1946; Neill and Dingwall, 1950; Macdonald et al., 1960; Lieberman et al., 1961; Lasser, 1972; Hernandez et al., 1975; Cunningham et al., 1978; Jin et al., 1979; Moyer et al., 1982]. Other consistently documented symptoms include enophthalmos, nystagmus, kyphosis, hypertension, stroke, and seizures. A large portion of CS patients are prone to dental caries. In this group, cavities occur in spite of brushing and regardless of eating habits or tube feeding. People with CS also have distinctive-sounding high-pitched voices.

CS patients are prone to pneumonia, and kidney and liver dysfunction also occur, especially in the later stages of the disease. The characteristics of CS may or may not be readily observable at birth, depending on the severity of the phenotype. In spite of their problems, people with CS tend to be outgoing and happy. Again, all these features have been consistently documented in the literature, including in the most recent review of CS [Nance and Berry, 1992].

Variation in Phenotype

CS has been described as having consistent clinical features that vary in severity [Proops et al., 1981]. The most severely affected individuals cannot sit independently or talk [Bender et al., 2003; Jaakkola et al., 2010], while those who are very mildly affected may learn to read and write at a third grade level or higher, ski or ride a

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bicycle, cook simple meals, or hold a job [Morris et al., 2007]. Others may not be aware that they have the disorder until well into adulthood, if at all [Miyauchi et al., 1994; Miyauchi-Hashimoto et al., 1998].

Because of the variation in phenotype, CS has traditionally been classified in three severity groups. They are currently called *Type I/Classic CS*, *Type II/early-onset CS*, and *Type III /Mild or Atypical CS*. Unfortunately, these names are not descriptive and can be confusing. For example, the numerical order of the types does not follow the order of severity. Confusingly for physicians, symptoms of Type I CS can be obvious at birth or soon after, making the Type II term *Early Onset* difficult to interpret. Type I is presumably called *Classic CS* because the first published case histories of CS described children who fit into this group [Cockayne, 1936; Cockayne, 1946]. Finally, the present study found that Type III/Atypical CS is not uncommon.

This study proposes a formal renaming of the groups, as follows:

- Severe CS (Type II or Early-onset CS)
- Moderate CS (Type I or Classical CS)
- Mild CS (Type III or Mild or Atypical CS)
- Photosensitivity only/adult-onset CS

The new names are more intuitive than the previous ones, and their use will reduce confusion among parents and clinicians. Each group can be further subdivided informally (e.g., *very severe*, *borderline moderate/mild*). Information in this article will help clinicians make informal subdivisions, such as "very severe" or "very mild." The first three groups (severe, moderate, and mild) may be thought of as *juvenile-onset CS*, as a further way of contrasting them with *adult-onset CS*.

People with adult-onset CS may be photosensitive throughout their lives and may also show one or more other symptoms associated with CS, such as very short stature [Hashimoto et al., 2008]. However, based on the scant information available at this time, this group is distinguishable from the juvenile-onset group by virtue of not experiencing other CS-type health problems until adulthood.

Progression

CS is a relentlessly progressive disorder. As they age, patients lose skills such as the ability to walk, stand, sit, crawl, self-feed, swallow, hear, and talk. Incontinence can occur in those who were previously continent. E.A. Cockayne's original articles are a good source for information on the progression of the syndrome over time [Cockayne, 1936, 1946]. Even the ability to support the head can diminish [Rapin et al., 2006]. Liver and kidney disease are common complications, [Rapin et al., 2006] and there are currently no CS-specific strategies for managing them. Additionally, as has been described extensively, vision and hearing loss are hallmarks of CS. Hearing aids and cochlear implants can be of significant help in improving quality of life after hearing loss [Morris et al., 2007]. Contractures progress to the point where feet turn inward; more rarely, they may cause hip dislocation. Surgery, Botox injections, and physical therapy can ameliorate problems related to contractures [Rapin et al., 2006].

Inheritance

CS is an autosomal recessive disorder. The majority of CS patients fall into two complementation groups: CS-A and CS-B. CS-A patients have mutations in the gene *CSA/ERCC8*, while *CSB/ERCC6* is mutated in the CS-B group. Most CS patients are in group B [Stefanini et al., 1996; Mallery et al., 1998]. *CSB* is part of a large protein complex that monitors the genome and facilitates DNA repair as needed [van den Boom et al., 2004].

Less frequently, CS or a similar disorder can also result from mutations in genes associated with xeroderma pigmentosum (XP). One type, called *XP with neurological disease*, is similar to CS. Two important differences between the two include cancerous skin lesions and tumors in the XP form (not seen in CS), and neuronal degeneration in the XP form compared to demyelinating neuropathy in CS [Kraemer et al., 2007]. Mutations in XP genes can also cause *XP/CS complex*, whose presentation is typical of CS [Lindenbaum et al., 2001].

The severe form of CS is also very similar to cerebro-oculo-facio-skeletal syndrome (COFS), a disease initially described among aboriginal people in western Canada [Lowry et al., 1971; Pena and Shokeir, 1974]. Studies have shown that the UV sensitivity profiles of fibroblasts from children diagnosed with CS are indistinguishable from fibroblasts from patients diagnosed with CS; furthermore, some COFS patients carry mutations in *CSB* [Meira et al., 2000; Laugel et al., 2008b; Jaakkola et al., 2010].

Overall, the genes involved in the neurological forms of XP include *XPA* (most common in Japan) [Kanda et al., 1990], *XPB* (*ERCC3*) [Oh et al., 2006], *XPD* (*ERCC2*) [Lehmann, 2001], *XPF* (*ERCC4*) [Moriwaki et al., 1993], and *XPG* (*ERCC5*) [Moriwaki et al., 1996]. Mutations in *XPD* can produce XP uncomplicated by neurological problems, XP with neurological disease, or trichothiodystrophy (TTD) [Lehmann, 2001]. TTD is similar to CS in that it involves photosensitivity, developmental delays, and other problems associated with CS [Kraemer et al., 2007; Faghri et al., 2008]. One important difference between them is very brittle hair and/or nails (common in TTD but not in CS). A recent review by Kraemer et al. [2007] provides an excellent overview of these diseases.

Incidence of CS

CS is extremely rare. Its minimum incidence in four countries in Western Europe (France, Italy, the UK, and the Netherlands) was recently estimated at 2.7 per million births in the overall population and at 1.8 per million births among indigenous Europeans [Kleijer et al., 2008]. There are no statistics related to the incidence of CS elsewhere, but overall numbers are likely similar. CS is more prevalent in a few geographical areas including Canada (including aboriginal residents of Manitoba [Lowry et al., 1971; Pena and Shokeir, 1974; Pena et al., 1978] and residents of Newfoundland), Japan, and certain middle Eastern and Western Asian countries [Kleijer et al., 2008].

Diagnosis

A major hurdle to diagnosing CS and managing it is the lack of a single recent source for information on the disorder. Although dozens of case studies exist in the literature, many are outdated and/

or hard to obtain. Many others were written by specialists and focus on single aspects of CS. Finally, to date, all multi-case reviews have obtained the vast majority of their data from the literature, and as a result, cannot provide a complete picture of CS. This problem was noted in the most recent review of CS, published in 1992 [Nance and Berry, 1992]. This study attempts to address this problem by using 45 previously undescribed well-documented cases that are supplemented by information from the literature.

Goal of This Study

To date, no study has provided an explicit description of each severity group in CS. As a result, important information for each group—such as life expectancy—has not been calculated or published. The goal of this study was to provide a comprehensive a description of each severity group in CS. These descriptions should help physicians determine which classification best fits a patient, which will in turn aid prognosis and management of the disorder.

MATERIALS AND METHODS

In order to gain as much information as possible about characteristics associated with each severity group, the author surveyed the families of 45 people with CS and obtained medical records whenever possible. Survey information was supplemented with data from the literature. The literature aided in classifying cases as severe, moderate, or mild and published case histories provided extra information on the characteristics associated with each severity group.

All methods in this study were approved by an institutional review board. Parents signed IRB-approved consent forms and answered an IRB-approved questionnaire.

Recruitment

Subjects were recruited in two ways. First, the author attended three annual CS family meetings, where verbal announcements about the survey were made. Parents were invited to approach the PI to discuss the survey, and questionnaires and consent forms were left on a table that also held other information for the families. Second, the Share and Care CS Network published announcements on the society's website and in newsletters. Information and questionnaires were displayed on the website with the author's contact information. Phone interviews and requests for medical records occurred after the completion of questionnaires.

Survey

Survey data came from questionnaires, medical records, extensive interviews with the families of CS patients, and visual observations in some cases. In six instances, families provided peer-reviewed articles describing their children. The survey sheet used by the author has been included as Supplementary Information.

All patients were given code names. Quantitative data for each person (height for age, age at death, etc.) were entered into a spreadsheet, which was used for calculations of averages and standard deviations. All data points were checked at least twice for accuracy. Information regarding centile rankings for height, weight, and head circumference was obtained from charts published by the U.S. Centers for Disease Control & Prevention.

Severity Group Classifications

Decisions about a survey patient's severity group were made by using the literature and patient medical records. Many individual CS case histories have been published; these publications were used to gain an initial understanding of the different phenotypes that occur in CS. Many articles contain explicit statements about the severity of a case, such as using the words *severe* or *mild* or *atypical* to describe a patient. Examples include, but are not limited to [Kennedy et al., 1980; Nishio et al., 1988; Lahiri and Davies, 2003] other articles made a patient's severity group clear in spite of not using explicit terms [Levin et al., 1983; Tinsa et al., 2009; Jaakkola et al., 2010]. Information that made a patient's severity group clear included photographs, data related to length- or height-for-age and head circumference, and descriptions of a patient's skills and abilities.

As hypothetical examples, a patient described as being unable to sit or talk or as having a head circumference of $\leq$40 cm (50th centile at $\sim$2 months) at age 3 years was determined to be in the severe group. Alternatively, a person classified as having the ability to walk independently who could speak a limited number of words (and may have had, e.g., the ability to combine 2–3 words, but rarely more) would be classified as moderately affected. Finally, a patient whose typical speech patterns included sentences of 6–7 words or more would be classified as mild. Mildly affected survey patients could typically recognize letters or write their names. The most mildly affected patients could read or write at a third grade level. These people could also perform relatively advanced gross motor skills, such as skiing or riding a bicycle.

Use of the Literature to Supplement Survey Data

Published case histories were also an important source of data for this study—particularly for life expectancy calculations. Although 45 survey patients is a relatively large number for a disease as rare as CS, the sample size is still very small by statistical standards. Because of this, calculations of life expectancy, height, and head circumference use information from the literature. Newsletters provided by the past president of the Share and Care Cockayne Syndrome Network were also sources of this information. Data from published sources were used if and only if it was possible to make a reliable decision about the severity of a patient's case.

RESULTS AND DISCUSSION

A total of 45 people responded to this survey (Table I). Extensive interviews with all parents and/or guardians were performed, and medical records were obtained or examined for 20 patients. Additional records were also examined during face-to-face meetings at annual gatherings for families of people with CS. In 18 additional cases, parents read excerpts from medical records over the phone. Excerpts included chronological data related to height, weight, and

TABLE I. Number of Surveyed Persons by Severity Group

Severity group	Number surveyed here
Severe	14
Moderate	16
Mild	15
Total	45

head circumference, results of CT and MRI scans, results of eye and hearing exams, diagnostic information, test results, etc.

Overview of Severity Groups in CS

As a general rule, the severity of CS is correlated with size, skill development, and life expectancy. More severely affected patients are smaller, learn the fewest skills, and have the shortest lives. Mildly affected patients are larger, learn many more skills, and have the longest life expectancies. At one extreme, the most severely affected children with CS do not grow larger than average-sized 6-month-old infants, cannot speak or sit up, and may die before age 4. At the other extreme, the most mildly affected patients may grow to well over 4 feet tall, may learn to ski, and may hold basic paid jobs. Members of this group may live into their 40s or beyond. Patients fitting both of these descriptions were surveyed for this study.

An important fact about CS is that there is no such thing as a typical (or "classic") CS patient. Rather, the phenotypes of CS exist on an overlapping sliding scale that goes from very severe (death before age 3) to very mild (death in the 40s or later). In spite of this fact, the vast majority of patients in this survey were easily classifiable as severe, moderate, or mild. Classifying one patient was difficult, and two others had characteristics of two severity groups, but assigning membership in one group was still relatively straightforward. These facts should be borne in mind by clinicians.

Severe CS

Children in this group have the shortest life expectancy (5.0 years) and are the smallest of all people with CS. The most severely affected survey subjects were the size of a 6-month-old infant at age 3 years or older, could not sit up, and could not speak. The less severely affected members of this group were larger (up to the size of an average 18 months–2-year-old child at age ~6–7 years) and were more communicative in that could sign or say a few words. Many in this latter subgroup could cruise on furniture or use a reverse walker. All children in this group were described by parents/doctors or observed by the author as happy and outgoing (Fig. 1).

Gross motor skills. Of 14 surveyed children in this group, 10 were unable to sit without support and one could sit for 1–2 min with careful supervision. The other could sit independently, though this skill was lost as the syndrome progressed. Severe flexion contractures were cited as a major barrier to sitting. No child in this group was able to walk independently. Parents and medical records cited upper body weakness and contractures as factors inhibiting gross motor skill development. Kyphosis was reported in 12 patients in this group; it also inhibited gross motor skill development. Observations about inability to sit or walk in severely affected CS patients have also been reported in the literature [Hallervorden, 1950; Lowry et al., 1971; Levin et al., 1983; Nishio et al., 1988; Jaeken et al., 1989; Bender et al., 2003; Sonmez et al., 2006; Laugel et al., 2008b].

FIG. 1. Patient 1 (here, 5 years, 11 months), severe/borderline moderate. "She was a living example of unconditional love who touched everyone she met." [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

There was some overlap between the less severely affected members of this group and the more severely affected children in the Moderate group. This overlap highlights the nature of CS as a disease with a continuous spectrum of severity.

Musculoskeletal abnormalities. Progressive flexion contractures were reported in all patients in this group. Kyphosis occurred in 12 patients out of 14.

Communication. Communication was extremely limited at best in severely affected children. For example, only four members of this group spoke a limited number of words (<10). None was able to combine two words, recognize letters, or write. These findings are consistent with the literature [Riggs and Seibert, 1972; Levin et al., 1983; Leech et al., 1985; Nishio et al., 1988; Patton et al., 1989; Hayashi et al., 1992; Bender et al., 2003]. Parents reported that their children created non-verbal ways of expressing needs, such as tapping a leg to indicate needing a blanket. Parents of

five children cited sign language as a means of communication, though the number of signs learned was limited (<30 in all cases, <10 in 3). Children with the most severe forms of CS were unable to use sign language.

Length and weight. Length data were available for 21 children (survey/literature) [Hallervorden, 1950; Schmickel et al., 1977; Moyer et al., 1982; Levin et al., 1983; Leech et al., 1985; Nishio et al., 1988; Jaeken et al., 1989; Patton et al., 1989; Hayashi et al., 1992; Bender et al., 2003]. The greatest length of a child in the severe group was 87 cm at autopsy in a boy from the survey, aged nearly 8 years (50th centile at age ~24 months). Measurements at a single age (6 years) were available for 6 children (4 survey, 3 literature; see Table II) [Leech et al., 1985; Jaeken et al., 1989]. The average length was 79 cm (50th centile at ~15 months for boys and ~16 months for girls).

Length/stature measurement in CS can be complicated by musculoskeletal deformities. For example, it appeared to fluctuate between checkups in four growth charts were obtained in this study. Two medical records noted that length measurement was complicated by contractures.

The weight of severely affected children is generally far below the 3rd centile for their ages. Precise data are not included here due to fluctuations, but children in this group did not exceed 13 kg/29 pounds at most (in a tube-fed school-aged survey child) [Hallervorden, 1950; Schmickel et al., 1977; Moyer et al., 1982; Levin et al., 1983; Nishio et al., 1988; Jaeken et al., 1989; Hayashi et al., 1992; Bender et al., 2003]. A better method for assessing body weight in may be to use weight-for-length. The most severely affected children were still underweight by this measure, but the gap was not as drastic as the one between a 5-year-old child with CS weighing 25 pounds and the expected weight of a healthy 5-year old.

As a rule, children in this group were poor eaters. Parents universally reported that delivering adequate nutrition was a major challenge. Lack of appetite was reported in all members of this group. This problem was frequently complicated by acid reflux (13/14 patients), chronic vomiting (12/14), or episodes of choking or gagging on food (11/14). Silent aspiration was also reported in 5/14 survey patients in this group. Parents also reported that common gastrointestinal ailments put their children at high risk for dangerous weight loss (≥10% of body mass in a matter of days). *Any CS patient with a gastrointestinal ailment should be seen by a clinician immediately.*

The use of feeding tubes was reported as an important and useful approach to these problems. Feeding tubes also eased challenges related to the delivery of medications and vitamins.

Tremors. Hand or other tremors were reported in 8/14 children in this group and among severely affected children described in the literature [Ohno and Hirooka, 1966; Schmickel et al., 1977; Hirooka et al., 1988].

Head circumference. Occipitofrontal head circumference (OFC) data were available in eight children surveyed in this study and from 21 published case histories [Riggs and Seibert, 1972; Moyer et al., 1982; Levin et al., 1983; Leech et al., 1985; Hirooka et al., 1988; Nishio et al., 1988; Jaeken et al., 1989; Patton et al., 1989; Choong et al., 1997; Laugel et al., 2008b].

Head size at birth was available for 17 children (5 survey/12 literature). One measurement noted in the literature was at the 75th centile—yet the child was hospitalized with microcephaly at 9 months [Jaeken et al., 1989]. The next largest OFC was just below the 25th centile (survey subject). The next 7 measurements were clustered around the 10th centile [Levin et al., 1983; Leech et al., 1985; Patton et al., 1989; Laugel et al., 2008b]. The next 5 clustered around the 5th centile [Leech et al., 1985; Jaeken et al., 1989; Laugel et al., 2008b]. Six were below the 3rd centile [Moyer et al., 1982].

In 22 children who were not infants, no measurement exceeded 42 cm (50th centile at ~4 months for boys and 5.5 months for girls) [Riggs and Seibert, 1972; Moyer et al., 1982; Levin et al., 1983; Leech et al., 1985; Hirooka et al., 1988; Nishio et al., 1988; Jaeken et al., 1989; Patton et al., 1989; Choong et al., 1997; Del Bigio et al., 1997; Bender et al., 2003; Laugel et al., 2008b]. The smallest measurement was 34.4 cm in a boy aged 2 years 8 months (3rd centile for 1 month), [Jaeken et al., 1989] and the largest was 42 cm in a girl in the survey aged 4.5 years. Head circumference did not exceed 39 cm in 13 children (50th centile for boys or girls aged ~2 months). An additional 9 patients with cerebro-oculo-facio-skeletal syndrome (COFS; see below) all had OFCs <40 cm [Pena and Shokeir, 1974].

Head growth ceased at ≤2 years in 6/6 survey patients for whom chronological data were available. These findings mirror those in published case histories reporting early cessation of either head growth [Riggs and Seibert, 1972; Leech et al., 1985; Nishio et al., 1988; Jaeken et al., 1989] or overall growth in severe CS [Moyer et al., 1982; Hayashi et al., 1992]. In three published cases, head growth stopped at 10 months [Patton et al., 1989], 16 months [Jaeken et al., 1989], and 18 months [Jaeken et al., 1989]. One report did not cite when growth stopped, but reported an OFC of 36.5 cm at 25 and 35 months (50th centile for ~2 weeks) [Nishio et al., 1988].

Average age at death. The average age at death in this group was 5.0 years, with a standard deviation of 2.0 years (Table III; range: 8 months–11 years). Reflecting the fact that CS phenotypes exist on a

TABLE II. Summary of Length and Stature by Severity Group in CS

Severity group/age	Average stature, cm (number)	Standard deviation (cm)	Range (cm)
Severe/6 years	79 (6)	5	75–87
Moderate/6 years	99 (9)	5	91–107
Mild/6 years	104 (7)	6	97–115
Moderate/16 years	104 (11)	8	94–118
Mild/16+ years	128 (18)	15	107–148

TABLE III. Age at Death in Different CS Groups

Severity group/age (total[a])	Mean age at death (years)	Median (years)	Standard deviation (years)	Range (years)
Severe (71)	5.0	5.0	2.0	0.6–11
Moderate (34)	16.1	16.0	3.2	11–22
Mild (15)	30.3	30.9	6.5	22–42[b]

[a]Life expectancy calculations included data from published case histories, as noted in the Materials and Methods Section.
[b]One living survey patient is currently 44-year old, and the life expectancy section for mild patients cites reports of living mildly affected CS patients in their 40s and 50s.

sliding scale, children surviving to age 7 tended to be the largest in this group, while those who died before age 4 tended to be the smallest. Severely affected children tended to be poor health for greater proportions of their lives in comparison those in other groups. This statement is supported by the literature [Schmickel et al., 1977; Moyer et al., 1982; Jaeken et al., 1989; Patton et al., 1989; Graham et al., 2001; Laugel et al., 2008b].

Age at death was calculated from survey data and published information (peer-reviewed literature as well as 18 newsletters provided by past directors of the Share and Care Cockayne Syndrome Network). Data from the literature and newsletters were used only if diagnosis, severity group, and age at death could be reliably determined. Sixteen published articles (some reporting multiple cases) contained information that was sufficient to determine that the subject had severe CS [Hallervorden, 1950; Riggs and Seibert, 1972; Pena et al., 1978; Moyer et al., 1982; Levin et al., 1983; Leech et al., 1985; Hirooka et al., 1988; Nishio et al., 1988; Jaeken et al., 1989; Patton et al., 1989; Hayashi et al., 1992; Graham et al., 2001; Falik-Zaccai et al., 2008].

Causes of death in severe CS. A cause of death was identifiable in 42 cases (15 survey/27 literature, including newsletters) [Riggs and Seibert, 1972; Pena et al., 1978; Levin et al., 1983; Leech et al., 1985; Hirooka et al., 1988; Nishio et al., 1988; Jaeken et al., 1989; Patton et al., 1989; Hayashi et al., 1992; Del Bigio et al., 1997; Powell and Meira, 2000; Graham et al., 2001; Laugel et al., 2008b]. The majority of children (26) succumbed to pneumonia or other respiratory ailments. The remaining deaths were due to kidney failure (6), complications of seizures (4), cardiac arrest (2), multisymptom complications of the disease (2), liver failure (1), and stroke (1).

Severe CS and cerebro-oculo-facio-skeletal syndrome (COFS). Recent data have shown that COFS is a very severe form of CS. COFS has been described as an autosomal recessive disorder similar to severe forms of CS and to MICRO syndrome, Neu-Laxova syndrome, etc. [Meira et al., 2000]. It was first reported in Manitobans of aboriginal background [Lowry et al., 1971; Pena and Shokeir, 1974]. Although one child diagnosed with COFS lived to age 11 [Meira et al., 2000], the disease typically involves extreme failure to thrive, with death usually at or well before age 5. In two recently reported cases, death was at 10 and 22 months [Laugel et al., 2008b]. Both cases were diagnosed as having mutations in CSB.

Other cases labeled as COFS have been due to mutations in CSB: to date, studies have found CSB mutations in 16 children diagnosed with COFS [Del Bigio et al., 1997; Meira et al., 2000; Powell and Meira, 2000; Laugel et al., 2008b]. Two COFS cases have been due to *XPD/ERCC2* mutations [Graham et al., 2001], one to *XPG/ERCC5* [Hamel et al., 1996], and one to *ERCC1* [Jaspers et al., 2007]. Autopsy findings in COFS have been consistent with CS [Dolman and Wright, 1978; Pena et al., 1978; Patton et al., 1989; Del Bigio et al., 1997].

Various authors have stated that COFS is a severe form of CS or overlaps with it [Sugarman, 1973; Patton et al., 1989; Powell and Meira, 2000; Kraemer et al., 2007; Kleijer et al., 2008; Laugel et al., 2008b]. Conversely, three reports have diagnosed CS in children whose facial appearances match COFS [Patton et al., 1989; Wooldridge et al., 1996; Choong et al., 1997]. Given the similarities between severe CS and COFS, as well as the abundant evidence of XP or CS gene mutations in COFS, COFS appears to be a severe form of CS rather than a distinct syndrome. Genetic testing can answer the question, and those with mutations in a CS gene should be diagnosed as having CS. Patient diagnosis and prognosis would be simplified if use of the term *COFS* is abandoned in this group in favor of *severe CS* or *very severe CS*.

Including COFS in the larger CS group is important not only for simplifying diagnosis and prognosis, but because it will aid families. There is no support group for COFS, and families who are unaware of its connection to CS may not contact support CS groups, leaving them to struggle alone.

Moderate CS

Survey subjects with moderate CS were generally larger than those with severe CS, met more milestones, and lived longer. Overall, the survey respondents in this group were distinguishable from the severe group by virtue of size (height, weight, and OFC) and the abilities to sit independently and self-feed, although 3/16 in this group learned <10 words. This fact reflects the fact that CS phenotypes exist on a sliding scale. The average age at death in moderately affected patients was 16.1 years.

Communication. Most members of the survey group (11/16) could combine 2–3 words. Two spoke in sentences of 5–6 words. Many supplemented verbal speech with sign language, with one learning >200 signs. Four members of this group could recognize letters or sight read a few words, including their names and other very common words such as "men." Two were able to write or type their names. Increased skills in this group allowed greater peer interactions compared to children in the severely affected group. Parents generally reported that their children enjoyed school and that their affectionate natures made them popular.

Mobility. All but one member of this group could sit independently. The child who could not sit independently was affected by severe contractures that precluded sitting or standing.

Independent walking occurred in 12/16 members in this group, if only for a few steps. All but one could also use a tricycle or sit-and-push toy. Standing, cruising, and walking all began well after the typical ages. For example, walking generally started past age 2 and as late as age 4. Late walking has also been documented in the literature (Neill and Dingwall, 1950). The ability to walk or stand was lost as the syndrome—especially contractures—progressed, though the age of skill loss varied among study subjects. Most moderately affected children described in the literature were able to walk alone [Cockayne, 1936; Neill and Dingwall, 1950; Macdonald et al., 1960; Norman and Tingey, 1966; Jin et al., 1979; Gandolfi et al., 1984; Schenone et al., 1986]; though a few needed assistance [Rowlatt, 1969; Soffer et al., 1979; Proops et al., 1981; Houston et al., 1982].

Musculoskeletal abnormalities. Progressive flexion contractures were reported in all patients in this group. Kyphosis occurred in 11 patients out of 16, and scoliosis occurred in 4 patients.

Stature and Weight. Of 25 people (survey/literature) for whom height data at age >4 were obtained, 10 were taller than 100 cm, and all but one were at least 90 cm tall [Macdonald et al., 1960; Lyon et al., 1968; Rowlatt, 1969; Srivastava et al., 1974; Cunningham et al., 1978; Soffer et al., 1979; Proops et al., 1981; Houston et al., 1982; Gandolfi et al., 1984]. In contrast, the length of the largest member of the severe group was 87 cm. Stature at 6 years was available for 9 people [Cockayne, 1936; Neill and Dingwall, 1950] and for 11 people at 16 years [Cockayne, 1946; Neill and Dingwall, 1950; Houston et al., 1982]. Table II shows that average height in this group was 99 cm at age 6 and 104 cm at age 16. These measurements correspond respectively to the 50th centile for ages $\sim 3^1/_2$ and $\sim 4^1/_2$ in both sexes. Thus, between the decade between ages 6 and 16, moderately affected children grew as much as a healthy child would have grown in 1 year. As in severe CS, measurements were complicated by musculoskeletal deformities.

The weight of moderately affected CS individuals in the survey was generally well below the 3rd centile for age. Although these patients tended to weigh more than severely affected children, most were still exceptionally small: all weighed <20 kg, and 4 never weighed more than 12 kg. This finding is reflected in the literature [Cockayne, 1936; Neill and Dingwall, 1950; Macdonald et al., 1960; Lieberman et al., 1961; Proops et al., 1981; Cook, 1982; Gandolfi et al., 1984; Boltshauser et al., 1989].

As with children in the severe group, parents reported that providing adequate nutrition to individuals in this group was a significant challenge. Lack of appetite and inability to eat more than small amounts of food at a single sitting were cited in all moderately affected survey patients. Other problems included acid reflux (11/16), choking and gagging (9/16), and chronic vomiting (9/16 patients). Additionally, parents indicated that their children were at extremely high risk for dangerous weight loss due to gastrointestinal ailments. *Thus, as with the severely affected patients, any moderately affected CS patient with a gastrointestinal ailment should be seen by a clinician as soon as possible.* As with severely affected children, parents reported that feeding tubes were an important and useful approach to problems related to nutritional intake.

Tremors and treatment options. Hand and other tremors were reported in 11/16 survey individuals and in 11 moderately affected children in the literature [Neill and Dingwall, 1950; Macdonald et al., 1960; Spark, 1965; Norman and Tingey, 1966; Lyon et al., 1968; Land and Nogrady, 1969; Rowlatt, 1969; Sugarman et al., 1977; Cook, 1982; Houston et al., 1982; Sugita et al., 1987; Boltshauser et al., 1989; Neilan et al., 2008]. Studies often them described as "coarse tremors" or "intention tremors." Two case studies of moderately affected individuals noted the absence of tremor [Jin et al., 1979; Soffer et al., 1979].

In the moderate and mild groups, tremors are a debilitating complication of the syndrome. They interfere with simple quality-of-life activities including play, dressing, and eating. They can also contribute to falls. A recent small trial in three CS patients found that carbidopa-levodopa relieved symptoms of tremor, allowing patients to regain lost skills [Neilan et al., 2008]. Although the size of the patient cohort was extremely small, carbidopa-levodopa therapy may be an option in CS.

Head circumference. OFC data at age 2 years 9 months or older were available for 28 moderately affected children (survey data/literature) [Cockayne, 1936, 1946; Neill and Dingwall, 1950; Macdonald et al., 1960; Spark, 1965; Norman and Tingey, 1966; Lyon et al., 1968; Srivastava et al., 1974; Hernandez et al., 1975; Sugarman et al., 1977; Brumback et al., 1978; Cunningham et al., 1978; Jin et al., 1979; Soffer et al., 1979; Proops et al., 1981; Houston et al., 1982; Gandolfi et al., 1984]. Ages ranged from 2 years 9 months to 21 years. All but three measurements were ≥42 cm (the greatest measurement in the severe group). The largest head circumference in the moderate group was 49 cm at ages 12 and 14 years in two brothers in the survey (50th centile for age 27 months); the smallest was 40 cm at autopsy in a boy aged 14 years 9 months (50th centile for age 2 months) [Soffer et al., 1979]. As with the severe group, head growth stopped young. In survey children for whom multiple measurements were available, it stopped by age 7 in 5/5 children[1] [Cockayne, 1946; Neill and Dingwall, 1950; Macdonald et al., 1960; Srivastava et al., 1974; Brumback et al., 1978; Proops et al., 1981; Houston et al., 1982].

Puberty. All individuals of the appropriate age showed pubertal signs, including growth of pubic hair, occasional erections in boys, and menstruation in girls. Menstruation was irregular and light among survey respondents. Pubertal signs have also been reported in the literature [Cockayne, 1946; Rowlatt, 1969; Soffer et al., 1979; Sugita et al., 1987; Tan et al., 2005]. Changes in muscle tone and deepening voices were not reported in moderately affected boys in the survey, although they were reported in the mild group. Undescended testes are common in boys with CS [Nance and Berry, 1992].

Average age at death. The average age of death in this group was 16.1 years (Table III; range: 11.5–22.3 years). This figure was determined from survey data, newsletters, and case studies published in the literature. Data were only used when diagnosis and severity group could be reliably determined [Macdonald et al., 1960; Norman and Tingey, 1966; Lyon et al., 1968; Rowlatt, 1969; Sugarman et al., 1977; Soffer et al., 1979; Proops et al., 1981; Houston et al., 1982; Gandolfi et al., 1984].

[1]This statement is also supported by the literature.

Causes of death in moderate CS. A cause of death was identifiable in 21 cases (10 survey/11 literature, including newsletters [Macdonald et al., 1960; Norman and Tingey, 1966; Lyon et al., 1968; Rowlatt, 1969; Sugarman et al., 1977; Soffer et al., 1979; Houston et al., 1982; Gandolfi et al., 1984]. Death was due to pneumonia/respiratory ailments in 10 cases. The remaining deaths were due to kidney failure (5), multi-symptom complications of the disease (2), complications from seizures (1), cardiac arrest (1), enteritis (1), and ''adrenal insufficiency'' (1).

Mild CS

Children and adults with mild CS share many traits with other CS patients, including very short stature, developmental disabilities, hearing loss, vision problems, and sun sensitivity (Fig. 2). However, the skills attained and average age at death (30.3 years) in mild CS are significantly increased over other groups. As a result, many in this group are not suspected of having CS until adulthood and/or after they have visited many physician specialists—if they are diagnosed at all [Inoue et al., 1997; Rapin et al., 2006]. The literature describes mild CS/CS in adults as atypical or rare [Kennedy et al., 1980; Nance and Berry, 1992; Rapin et al., 2006; Morris et al., 2007; Hashimoto et al., 2008], yet the even distribution of severity group membership among survey subjects here (Table I) implies that mild CS may be under-diagnosed.

Communication. All mildly affected survey subjects spoke in sentences of 6–7 words or more. Three medical records described speech as slow, scanning, or dysarthric; these terms have been used in the literature as well [Miyauchi et al., 1994; Ellaway et al., 2000]. Many parents described their children as having good memories of past events, vivid imaginations, and in two people, a knack for making up stories. All could sight read letters, their names, or a small number of words, and four were able to read/write at a second grade level or higher. Some parents reported teaching sign language to their older children as hearing loss began.

Mobility. All mildly affected survey individuals could walk and all but one could run. In older patients, these skills had been lost as the syndrome progressed, but identifying a precise age at which decline began was not possible because the syndrome progressed differently in each subject.

Medical records for one person indicated earlier-than-average walking at 12 months, though most in the survey or the literature walked in the late-normal range [Hamdani et al., 2000; Rapin et al., 2006]. Seven survey subjects acquired advanced gross motor skills such as riding a bicycle without training wheels, skiing independently, or swimming a stroke independently.

FIG. 2. Patient 2, very mild. A: 18 years and B: 21 years. This individual was never cachectic and inadequate food intake was never a problem for her. Tooth extraction and braces reduced malocclusion. "She loved to swim, ride bikes, take walks, and shop. She would tell everyone 'I was born to shop'." [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

Musculoskeletal abnormalities. All mildly affected survey subjects individuals suffered from flexion contractures, a problem that has also been reported adult CS patients in the literature [Rapin et al., 2006]. Kyphosis was reported in 7 mildly affected survey patients and scoliosis occurred in 3.

Stature and weight, and eating habits. Table II shows overall average height at 6 years and at age 16 or older. The first group consisted of 8 survey subjects and 1 published case [Cockayne, 1936]. Average height was 104 cm (50th centile for age $\sim 4\,^{1}/_{2}$ in both sexes).

The overall average for the adults was 128 cm. Males (n = 11), averaged 131 cm (50th centile for age $\sim 8\,^{1}/_{2}$ years) [Smits et al., 1982; Fryns et al., 1991; Nance and Berry, 1992; Miyauchi et al., 1994; Ellaway et al., 2000; Komatsu et al., 2004]. Females (n = 8) averaged 127 cm (50th centile for age ~8 years) [Brumback et al., 1978; Kennedy et al., 1980; Miyauchi et al., 1994; Inoue et al., 1997; Lahiri and Davies, 2003; Hashimoto et al., 2008].

Members of this group tended to have the best overall eating habits with the greatest weights, with three survey individuals even being overweight. In general, parents did not report significant problems related to nutritional intake, although two reported using nutritional drinks as supplements. Weight loss and the need for tube feeding was reported in older individuals who had lost the ability to eat (one survey subject/literature) [Inoue et al., 1997; Komatsu et al., 2004]. This problem correlates with changes due to progress of the syndrome.

Most people in the survey experienced appetite loss and lost the ability to chew and/or swallow as the syndrome progressed; this problem has been reported in the literature as well [Inoue et al., 1997; Komatsu et al., 2004; Rapin et al., 2006]. Adults with mild CS are at increased risk of aspirating food as they age. For example, one survey subject in this group died of aspiration pneumonia, and choking concomitant with overall deterioration was reported in two others. Choking had been a lifelong problem in three further patients in this group.

Tremors. Tremors were reported in 15/15 individuals in the mild survey group. Tremors had the most profound effects on daily life in mildly affected survey patients. They typically interfered with fine motor skills and made patients prone to tripping and falling. In the literature, seven studies described 10 adults or older children with tremors [Kennedy et al., 1980; Smits et al., 1982; Fryns et al., 1991; Miyauchi et al., 1994; Inoue et al., 1997; Ellaway et al., 2000; Rapin et al., 2006].

In this group, tremors may adversely affect scores on intelligence tests, especially when the tests involve use of fine motor skills, such as stacking blocks or writing. As an example, one parent indicated that her child knew *how* to stack blocks but could not make a tower due to tremors. Parents also reported wide variation in the IQ scores for individual children, with scores going up and down without any noticeable gain or loss of abilities.

IQ and Testing. In one published report, cognitive deficiencies were not apparent at age 6, and became evident at ages 8–9 [Fryns et al., 1991]. IQs in the mild group have been measured in the borderline range (70, 74, 75, 77, 78) [Kennedy et al., 1980; Smits et al., 1982; Miyauchi et al., 1994]. Survey data and the literature indicate that IQ declines as the syndrome progresses [Smits et al., 1982].

Head circumference. OFC data were available for 13 mildly affected individuals (8 survey subjects and the literature) [Fryns et al., 1991; Miyauchi et al., 1994; Ellaway et al., 2000; Rapin et al., 2006]. Measurements were taken at ages 8 and up. Measurements in this group averaged 49.3 cm (range: 44 cm at 8 years–56 cm at 55 years).

Puberty and fertility. Pubertal changes were reported in every child who had reached the appropriate age. In girls, menstruation was often irregular and light. In boys, changes in muscle tone and deepened voices were observed by the study author, reported by parents and have been described in the literature [Fryns et al., 1991; Nance and Berry, 1992; Miyauchi et al., 1994; Ellaway et al., 2000; Hamdani et al., 2000]. In girls, breast and pubic hair growth occurred (survey/literature) [Crome and Kanjilal, 1971; Kennedy et al., 1980; Inoue et al., 1997; Lahiri and Davies, 2003]. Parents reported mood changes and increased interest in members of the opposite sex in their adolescent children. No woman in this survey was old enough to enter menopause; it was reported at 38 years in one published study [Inoue et al., 1997].

Successful pregnancy has been reported in two cases of mild CS [Kennedy et al., 1980; Lahiri and Davies, 2003]. In one patient, a miscarriage occurred in a first pregnancy, and the mother's very small size complicated a second pregnancy. This woman received close in-hospital care beginning at 18 weeks gestation and gave birth to a healthy boy at 34 weeks [Lahiri and Davies, 2003].

Decline. As the syndrome progresses, mildly affected adults with CS experience the same problems as other CS patients. These include loss of mental and motor skills, progression of neurological abnormalities, weight loss, hearing loss, vision loss, increased susceptibility to infection and longer recovery times, and increased episodes of choking.

Decline occurred at varying ages among survey respondents. For some, loss of ambulatory skills, decreased energy, or loss of interest in hobbies began as early as age 6. In others, these problems did not begin until the late teens or early 20s. The age at which decline began did not appear to correlate with life expectancy. One person, who is currently one of the two oldest CS patients known to the author, began to lose ambulatory skills at age 6/7, but did not fully lose the ability until age 21. His sibling was able to ride a bicycle until age 33 and walked until age 37.

Hearing Loss. Hearing loss is progressive in CS and is a major problem affecting quality of life. Parents in this study reported that hearing loss often occurred suddenly (''he woke up deaf one morning'') or over 2–3 days. Loss of hearing is a significant event and, especially because it can happen suddenly in CS, can be a cause of significant anxiety. Parents reported that post-hearing loss children would become withdrawn and unhappy. In some patients, cochlear implants can improve quality of life and reduce anxiety [Morris et al., 2007].

Life expectancy. The average age of death in the mild group was 30.3 years, with a wide range (survey/literature; Table V) [Crome and Kanjilal, 1971; Brumback et al., 1978; Shemen et al., 1984; Inoue et al., 1997; Rapin et al., 2006; Morris et al., 2007]. A cause of death was identifiable in 6 cases, including 1 from the literature. They were pneumonia/respiratory ailment: 3; cardiac arrest: 1; liver failure: 1; and status epilepticus: 1 [Crome and Kanjilal, 1971].

The literature describes mildly affected adults with definitive diagnoses of CS at the ages of 35 [Komatsu et al., 2004], 42 [Miyauchi et al., 1994], 47 [Hashimoto et al., 2008], and 55 [Miyauchi et al., 1994]. Each of these individuals was in the CS-A or CS-B complementation group. Other individuals with likely diagnoses of mild CS were aged 14–28 (4 siblings) [Hamdani et al., 2000], 24 [Fryns et al., 1991], 25 [Kennedy et al., 1980], 37 [Boltshauser et al., 1989], 40 [Adachi et al., 2006], and 39–40 [Morris et al., 2007]. A recent review article presents an excellent overview of CS in adults [Rapin et al., 2006].

CS With Sun Sensitivity Only/Adult Onset CS

Two reports have described individuals aged 13 and 33 who carry null mutations in ERCC6/CSB [Miyauchi-Hashimoto et al., 1998; Horibata et al., 2004]. Each was completely healthy apart from abnormal sensitivity to UV light, and each was originally diagnosed with UV sensitivity syndrome. Both carry the same mutation in exon 2 of the CSB gene (CGA^{308}:Arg^{77} to TGA^{308}:stop) [Horibata et al., 2004; Hashimoto et al., 2008]. This mutation is a null mutation and is the same one found in a woman in whom CS symptoms began in adulthood. Apart from photosensitivity and very short stature, symptoms of CS did not appear in this patient until age 47 [Hashimoto et al., 2008]. Her symptoms included progressive hearing loss, dementia, and ataxia, as well as intracranial calcifications and cerebellar atrophy.

These studies suggested that this form of CS may be due to null mutations. However, another study of two children with severe CS found null mutations in the non-coding region of exon 1 and upstream regulatory sequences [Laugel et al., 2008a]. CSB mRNA and protein were undetectable in these children; they died aged 6 and 8. Thus, the adult-onset form may be caused by a particular null mutation the individual mutation may be most important.

Two individuals with mutations in *XPF* (*ERCC4*) have also been diagnosed with an adult-onset disease called *XP with neurological abnormalities*.[Moriwaki et al., 1993; Sijbers et al., 1998] Symptom onset began at ages 44 and 47. Both individuals experienced mental deterioration, progressive dysarthria and gait ataxia, choreiform movements, and cerebral atrophy. Both had a near-lifelong history of photosensitivity. Cerebellar atrophy and impairment of central nerve conduction were observed in one, and enlarged ventricles were found in the other.

General Points About CS

CS is a group of disorders of varying severity that varies from lethality within the first few years of life to apparent dormancy until middle age (Fig. 3). The form of CS that occurs early in life may be described as *juvenile-onset CS* to distinguish it from the form that occurs in adults (*adult-onset CS*). The juvenile form of the syndrome is characterized by dwarfism, photosensitivity, sensorineural hearing loss, microcephaly, developmental delays, contractures, and an outgoing personality. Other problems, which are outlined in Table IV, occur commonly in CS patients, but do not occur universally.

Juvenile-onset CS is characterized by three severity groups and identifying the group to which a patient belongs can aid prognosis. In general, severity groups correlate with size, milestones met, and life expectancy. For example, children in the severe group are the smallest of all CS patients and meet the fewest milestones (Table V for details). Average age at death, at 5.0 years, is the lowest of all the groups. These children typically cannot talk or walk independently. Moderately affected children are bigger than severely affected children (Table V). They usually learn to speak and may combine 2–3 words. Most children in this group learn to walk independently, if only for a few steps. Finally among the juvenile-onset group, mildly affected patients generally grow more, do more, and live longer.

Although symptoms of CS vary in severity, the same manifestations occur in all patients. For example, everyone in this survey shared photosensitivity, microcephaly, contractures, skill loss, and gait ataxia (in those who could walk). They were all generally outgoing and most were described by their parents as happy, although anxiety occurred in some as the disease progressed and skills—especially hearing—were lost. Progressive sensorineural hearing loss is likely universal in CS, though it may not occur until a patient's condition declines.

Variation in microcephaly is an example of variation in CS that correlates with severity. At one extreme, the head circumference of a severely affected survey child was 38 cm at 3.0 years (~7 standard deviations below the mean), while that of a very mildly affected 13-year old in the survey was ~51 cm (~2 standard deviations below the mean). The severely affected child was never able to talk or sit independently, and died at age 3.5 years. The mildly affected teenaged patient spoke in full sentences, could read, write, and partake in most activities common to children of her age. The severity of photosensitivity was a notable exception to this rule. Additionally, dental caries occur widely in CS, this study found no correlation between severity group and this problem.

On rare occasions, the lack of one or more of the problems found universally in this survey has been noted in the literature. For example, head circumference can be normal in patients with the form of CS that manifests as photosensitivity without other signs (until, possibly, middle age) [Miyauchi-Hashimoto et al., 1998]. In addition, one

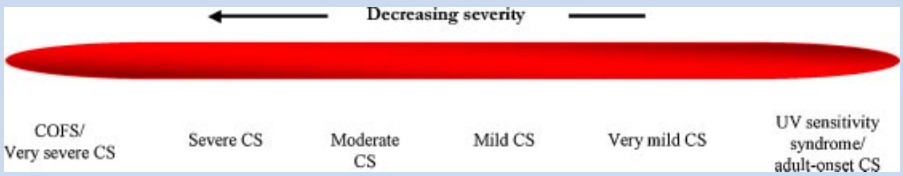

FIG. 3. CS has a continuous spectrum of severity. Life expectancy and acquired skills increase as severity decreases. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

TABLE IV. Summary of Symptoms/Attributes in CS Survey Patients

Problems or attributes reported in all survey patients. Cold extremities, contractures, developmental delays (cognitive, fine, and gross motor, language), gait ataxia in those who could walk, outgoing or happy personality prior to decline, microcephaly, photosensitivity (ranging from mild to extreme), pubertal changes in those of appropriate age, very short stature

Problems or attributes reported in >2/3 of survey patients (#). Hearing loss, including progressive hearing loss (43)[a], brain calcifications (37), hand tremors (36), nocturnal lagophthalmos (35), white matter abnormalities (34), dry eyes/lack of tears (33), kyphosis (30)

Problems or attributes reported in 1/3–2/3 of survey patients (#). Acid reflux (27), brain atrophy (27)[b], choking/gagging (26)[c], dental caries (26), chronic vomiting (24), cataracts (24), healthy shiny hair (24)[d], liver abnormalities (22), nystagmus (20), retinopathy (21), seizures (21), hypertension (20), generalized itchiness (19)

Problems or attributes reported in ~10% to 1/3 of survey patients (#). Birthweight <5th centile (13), eyes: dilation poorly inducible (13); leg cramps (10), ankle clonus (9), kidney abnormalities (9), EEG abnormal (8; not measured universally), scoliosis (7), strokes (7; all had been diagnosed with hypertension), silent aspiration (6), diabetes (5), BMI normal or above (4; all in Mild group)

The table shows the prevalence of symptoms and attributes among all CS patients surveyed here as a single group. Unless otherwise noted, symptoms were distributed broadly across all patient groups. This table is provided as a way to help provide a snapshot of the relative distribution of characteristics and problems associated with Cockayne syndrome.

[a]Likely present universally as the syndrome progresses; there were two unknowns.
[b]Likely present in >2/3; status of brain atrophy in several patients was unknown.
[c]Occurred chronically in 20 patients, and in six others as the disease progressed.
[d]Hair loss occurred in 17 patients as the syndrome progressed.

report of a 55-year-old adult with CS noted that the patient's head circumference was 56 cm, which was in the normal range [Miyauchi et al., 1994]. However, this study provided insufficient information to determine if this individual had the adult-onset form of CS. This is one limitation of the relatively small sample size of this study.

In addition, CS without apparent clinical photosensitivity has been reported [Meira et al., 2000; Laugel et al., 2008b; Tinsa et al., 2009]. However, biochemical testing of fibroblasts from these patients showed that their fibroblasts were indeed sensitive to UV light. There is no explanation as to why a patient with biochemical sensitivity to UV light would not also show clinical signs of the problem, nor is there any explanation for why photosensitivity varies as it does among CS patients.

Table IV summarizes symptoms and attributes that define CS, grouped by how often they occurred in patients surveyed for this

TABLE V. Summary of Characteristics of CS Patients by Severity Group

Characteristic	Severe	Moderate	Mild	Adult-onset[a]
Average length/ stature (cm)	6 years: 79 <~90 overall	6 years: 99 16 years+: 104[b]	6 years: 104 16 years: 128[b]	Normal?
Head circumference (cm)[c]	<42	<~49.5	>~47	Normal?
Speech/vocabulary	No or very few words	May combine 2–3 words	Conversational vocabulary; may combine 5–6+ words	Normal, but lost after syndrome progresses
Independent walking	Unlikely; cruising or walker use possible in some	Minimal, very late onset (age 2–4 years)	All can walk, many can run	Normal, but lost after syndrome progresses
Eating habits	Poor; likely able to eat soft foods only; tube feeding typically necessary	Poor; able to eat a wider variety of foods; tube feeding eventually necessary	Fair to good. Some in this group may not be cachectic or even slender	Normal
Pubertal changes	n/a	Periods/erections occur, few if any secondary sex characteristics	Periods/erections; secondary sex characteristics often present; pregnancy has been reported	Normal
Mean age at death, years	5.0	16.1	30.3	Cannot be calculated

[a]Minimal.
[b]Growth had stopped by age 16 or well before in all cases.
[c]Recorded when a child's head had stopped growing (between ages 2 and 3 in the severe group, generally between ages 7 and 10 in the moderate group, although cessation as early as age 3.5 was recorded in one patient, and as late as 14 years in mild patients, but as early as age 6.

study. The top section of the table shows symptoms that were present universally and are likely present in every case of juvenile CS. However, an apparent absence of clinical photosensitivity does not preclude the problem at a biochemical level. Although hearing loss was not reported in two survey patients, this problem is likely universal in CS. As of the survey period, two patients had not been suffered hearing loss, but both of their elder siblings had. Attempts to contact these two families were not successful.

In spite of the variation in the severity of their symptoms, most CS patients can be easily classified as members of a severity group. Physicians should be aware, however, that occasional patients may have characteristics of two groups.

The overall course of disease is broadly similar between different groups: patients initially grow and gain skills, then plateau, and finally lose skills and abilities. They experience progressive vision and hearing loss, loss of mobility, increased dysphagia, increased tremors, and loss of verbal and cognitive abilities. The length of each stage varies by group and individually.

Mutations in the gene *CSB* are involved in the majority of cases of CS [Neilan 2006], in many very severe cases classified as COFS [Meira et al., 2000; Powell and Meira, 2000; Laugel et al., 2008b], and in the apparently paradoxical cases in which symptoms do not become apparent until well into adulthood, if at all [Miyauchi-Hashimoto et al., 1998; Horibata et al., 2004; Hashimoto et al., 2008]. To date, past one mutation identified in patients with the adult form of CS, no genotype–phenotype correlations have been found.

Table V summarizes the findings of this study and provides guidelines for assigning a patient to a severity group. It is important to stress that although most individuals fit into one group, there is crossover between them. Thus, the guidelines are not absolutes. Additionally, the very small number of case histories regarding adult-onset CS/CS mutations with sun sensitivity means that a full description of this form of CS must wait until more information is available.

IMPORTANT SUMMARY POINTS ABOUT SYMPTOMS ASSOCIATED WITH CS

Congenital Cataracts Do Not Correlate With Poor Prognosis in CS

Congenital cataracts has been cited as a poor prognostic indicator in CS [Nance and Berry, 1992]. This survey found that although congenital cataracts are more likely to occur in severe cases of CS (7/14 severely affected survey subjects), the problem also occurs in moderate (3/16), and mild forms (2/15) of CS.

Furthermore, the two longest-lived persons in the survey (currently aged 42 and 44) were born with congenital cataracts, and all three persons in the moderate group lived 2 years beyond the average in that group. Two of the severely affected children lived 2.5 and 3.5 years past the average in their group.

Cataracts developed at later ages in an additional 11 patients. Again, occurrence was distributed across all severity groups, providing no correlations in this study between cataracts and severity of CS.

Photosensitivity Does Not Correlate With Severity Group in CS

Although photosensitivity is universal in CS, its severity varies. This study found no correlation between degree of photosensitivity and disease severity. There were severely and mildly affected survey patients with severe photosensitivity (defined as avoiding UV light at all costs). Mild photosensitivity (defined as being able to spend time outside when wearing sunscreen) also occurred in both of these groups. Moderately affected patients were also split this way.

Weight Loss Due to Gastrointestinal Ailments May Be Severe

This study confirmed past observations that CS patients tend to be poor eaters. This statement is especially true for patients in the severe and moderate groups, who were universally reported to have poor appetites at best.

Problems related to inadequate nutrition were frequently complicated by vomiting, acid reflux, and episodes of choking or gagging. These problems put CS patients at high risk for dangerous weight loss due to common gastrointestinal ailments. In addition, their poor eating habits make weight re-gain difficult. Therefore, any child with CS and a gastrointestinal ailment should be monitored immediately and closely.

Diagnosis

The Genetics Diagnostic Laboratory at Children's Hospital Boston is a CLIA-certified laboratory that provides diagnosis of CS. It is the only diagnostic laboratory in the U.S. for CS. Diagnosis is through sequencing the genes *CSA* and *CSB*; *XPA* can also be sequenced. This service is useful for all persons suspected of having CS. It may be especially useful for those diagnosed with related diseases who do not appear to be clinically photosensitive.

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