Cockayne Syndrome:
A Manual for Healthcare Providers

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Dedication

Cockayne Syndrome: A Manual for Healthcare Providers is dedicated to all of the clinicians who see, treat and are inspired by our Cockayne Syndrome (CS) children, and to the parents and caregivers who provide respite and loving care for them.

To all of the parents around the world who have walked this path daily, shedding light and working so feverishly to get information as well as support and advocate for CS research: we thank you. For the families who have children living with CS: we walk beside you. For the families who received a recent diagnosis: we know the grief you experience, but we are grateful that you have found this manual. We understand the path you walk, and you are never alone.

The dream to compile this comprehensive manual was inspired by many CS parents and children/angels around the world. The hope is to have a go-to resource providing guidance for clinicians and the medical team, and support for parents and caregivers. Many of our CS angels sacrificed for lessons our future CS kids will benefit from. Their lives were never in vain.

Sincere thanks to many CS parents around the world who came together to provide feedback on what would be necessary to include in this manual. We would like to specifically acknowledge Amy Marini, Haylee Carroll, Nikki Cohen, Missy Miller, Christina Polchin, and Maria Pellicane—all of whom are CS Moms with the power to get anything done that they put their minds to.

And to our Clinical Advisory Board Members: without you and your amazing contributions, this manual would not have ever taken the form that it is before us. We are forever grateful for all of your hard work. We know that this manual is not the end of your CS work—that children not even diagnosed yet will benefit from all of your research and expertise for years to come.

Additionally, we would like to acknowledge Thistle Editorial LLC, who provided assistance with content development.

Lastly, we offer our thanks to the National Initiative for Cockayne Syndrome, without whose support and stewardship, this manual would never have been completed.

National Initiative for Cockayne Syndrome Clinical Advisory Board

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Overview

Background

First reported in 1936,[1] Cockayne syndrome is an inherited autosomal recessive disorder caused by defective DNA transcription or repair, such as chromosomal breakages and interchanges that are either spontaneous or occur in response to DNA-damaging agents.[2] In the United States and Western Europe, the incidence of Cockayne syndrome is estimated at 2.7 cases per million births.[3,4] The condition appears to affect both sexes with a male-to-female ratio of 1:1 and is similarly prevalent across racial and ethnic groups (panethnic).

Clinical Type and Prognosis

Cockayne syndrome spans a phenotype spectrum that is classified into three main types, affects multiple systems, and varies widely in clinical manifestation.[5,6]

- **Type I.** Children with Cockayne syndrome I typically present in the first decade of life with characteristic somatic and facial features that include a butterfly rash, sunken eyes, and nasal atrophy. Progressive sensorineural deafness is also typical. Cockayne syndrome I is associated with mental impairment, progressive neurologic degeneration, microcephaly, and growth failure over time. Children with this condition have an increased risk of infections. Unremitting, progressive neurologic degeneration usually leads to death in the second or third decade of life.
- **Type II.** This is the most severe type and typically manifests at birth or infancy and has a worse prognosis than Cockayne syndrome I. Mean age of death is 7 years.[3,7]
- **Type III.** This is the least severe type of Cockayne syndrome and is often diagnosed during or after adolescence.[8] Type III is characterized by cognitive impairment, progressive cerebellar symptoms, and hearing loss. Patients might have photosensitivity, intellectual disability, and learning difficulties.
- **Xeroderma pigmentosum-Cockayne syndrome complex (XP-CS).** This is a very rare disorder that combines clinical features of XP with CS. XP-CS patients typically experience the cutaneous features of xeroderma pigmentosum and the neurodegenerative features of CS. XP-CS is typically diagnosed in the first five years of life in which children grow and acquire skills, plateau, and then decline.[7] These patients may also develop a form of leukodystrophy called tigroid demyelination, in which small patches of preserved myelin occur within demyelinated areas.[7]

Although CS type I predominately tends to involve mutations in *ERCC8* and CS type II tends to involve mutations in *ERCC6*, this is not always the case. In general, mutations in *ERCC6* (which encodes for Cockayne syndrome B protein [CSB]) tend to be more severe, but some patients with *ERCC6* mutations are classified as the less severe type I CS. The reverse can be true for *ERCC8* mutations. A retrospective study (n = 45) reported that 36% of patients were diagnosed with type I, 31% with type II, and 33% with type III.[9]

By comparison, XP-CS is extremely rare and is associated with severe photosensitivity and lesions caused by ultraviolet (UV) light, increased risk of skin cancer, and severe somatic and neurologic features, including hearing loss, joint contractures, and dislocations.[10,11]

Cerebro-oculo-facial-skeletal syndrome (COFS), which is also a part of the spectrum of Cockayne syndrome, is similarly rare. Caused by CSB or XPD dysfunction, COFS shares several characteristics of CS type II.[12] Infants with COFS have intrauterine or very early growth failure with microcephaly, enophthalmos, eye abnormalities, and intellectual impairment.[12]

Life expectancy for children with CS continues to improve as this condition is becoming better understood and symptomatic therapies emerge and are used more effectively.

Clinical Manifestations

Cockayne syndrome is associated with premature aging, progressive dementia, deafness, intellectual disability, cachexia, microcephaly, loss of adipose tissue, and characteristic facies and ocular problems.[6] Diffuse demyelination of the central nervous system and peripheral nerves lead to progressive neurologic deterioration, such as kyphoscoliosis, gait impairment (eg, limb ataxia), and tremors. Retinal degeneration (pigmented retinopathy and atrophy) and photosensitivity contribute to considerable neurologic dysfunction.[13] Over 60% of patients with Cockayne syndrome have a “salt and pepper” retinal degeneration that is considered one of the characteristics of the disease.[2] Approximately 50% of patients have sensorineural hearing loss. Cockayne syndrome is also associated with polyneuropathies, such as sensorimotor demyelinating polyneuropathy, and an increased tendency to develop malignancies.[14] Many children across phenotypes develop dementia. Death is often precipitated by profound cachexia, intercurrent illness, or hypertensive vascular disease.[15]

Evaluation

Children with Cockayne syndrome can present with failure to thrive and any of the following characteristics: delayed psychomotor development, growth failure, photosensitive rash, and cataracts. Clinicians should conduct a thorough evaluation of children for whom they suspect Cockayne syndrome to confirm diagnosis, exclude differential diagnoses, and establish disease severity. Diagnosis is established via

Table 1. Potential Findings on Evaluation[3, 11,12,15,17]

Physical	
Musculoskeletal • Microcephaly, short stature, and long limbs with joint contractures • Thin nose, large ears, sunken eyes • Cachexia • Large hands and feet	**Dermatologic** • Photosensitive dermatitis (erythema, scale) • Hyperpigmentation, atrophy, and telangiectasia • Cyanotic acral edema of extremities • Nail dystrophies, hair anomalies • Reduced subcutaneous fat
Neurologic • Ataxia, tremors, and gait impairment • Progressive sensorineural deafness • Mental retardation	**Ophthalmologic** • Salt and pepper retinal pigmentation • Miotic pupils, cataracts, optic atrophy, corneal opacity, and nystagmus
Endocrinologic • Hypogonadism with micropenis in boys and irregular menses in girls • Diabetes and insulin resistance	**Dental** • Caries • Delayed eruption of deciduous teeth
Imaging	
• Increased ventricular size, cerebral atrophy, or both • Calcifications in basal ganglia • Demyelination of subcortical white matter • Thickened calvarium • Small sella turcica	• Biconvex flattening of vertebrae • Sclerotic “ivory” epiphyses, especially in fingers • Squared-off pelvis with hypoplastic iliac wings • Kyphosis, osteoporosis

molecular testing and identification of biallelic pathogenic variants in *ERCC6* or *ERCC8*.[16]

Laboratory studies, such as skeletal radiography, and chromosomal breakage studies can help to exclude other disorders, such as UV-sensitive syndrome, Werner syndrome, and xeroderma pigmentosum. In addition to developmental evaluation to determine appropriate supportive services and educational resources, the following specialties are typically involved in the evaluation and management of children with Cockayne syndrome:

- Dentistry
- Gastroenterology
- Genetics
- Ear, nose, and throat/audiology
- Neurology
- Nutrition
- Ophthalmology
- Physical therapy

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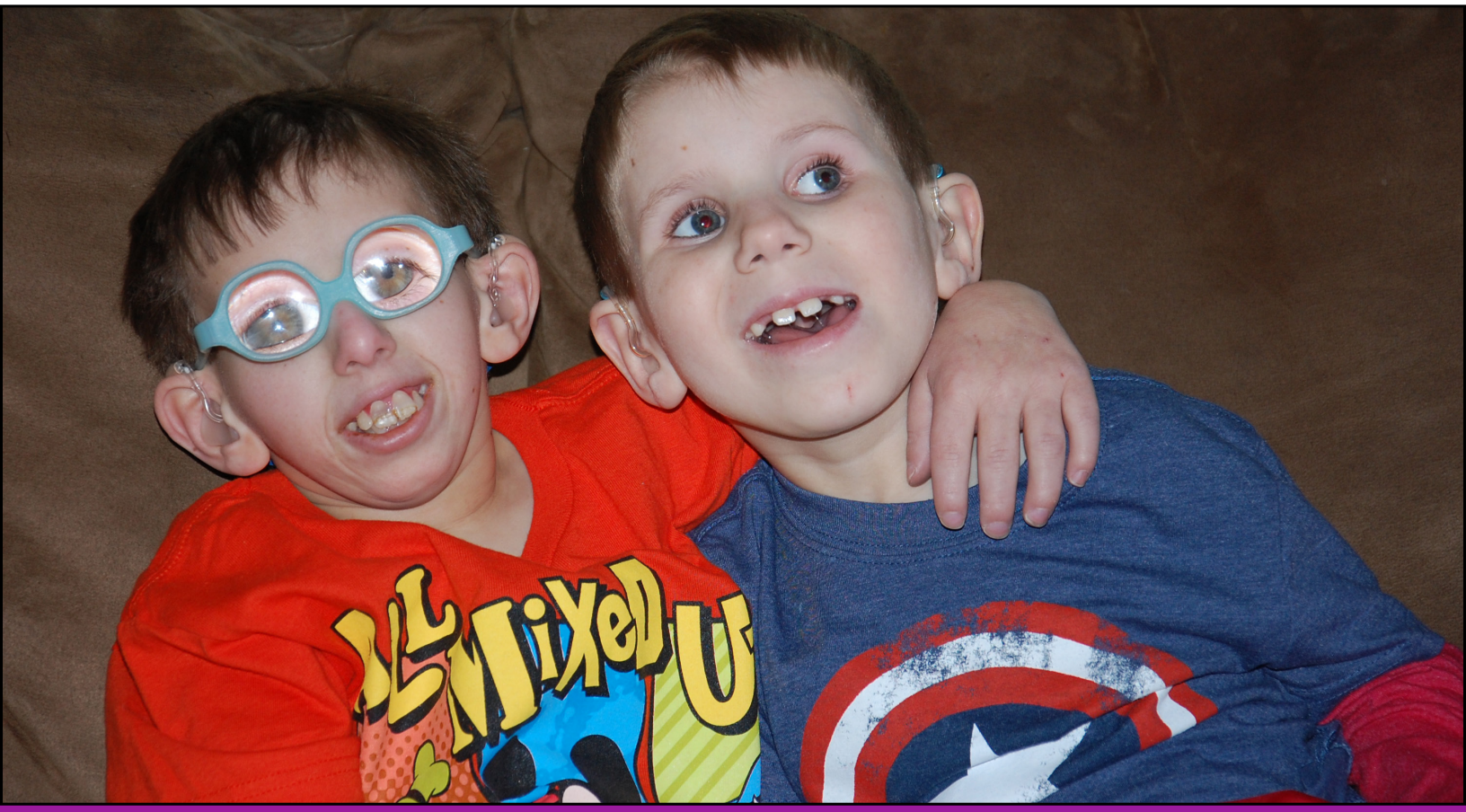

Audiology

Hearing Loss Type and Pattern

Progressive hearing loss is a cardinal characteristic of Cockayne syndrome. Hearing loss occurs as a consequence of atrophy at multiple sites along auditory pathways and hair cell loss in the basal turn of the cochlea.[1] Inner and middle ear anatomical abnormalities are also thought to contribute to conductive deafness.[2] Hearing loss type and pattern vary and can be sensorineural, conductive, or mixed. Studies suggest that hearing loss in children with Cockayne syndrome is typically bilateral, sensorineural, and progressive,[2-4] with type and pattern of hearing loss ranging from mild, late impairment to profound neonatal hearing loss.[2,3] Regardless of the type and pattern, without early diagnosis, any decline in auditory function can lead to deficits in language, communication, and cognitive skills as well as social isolation.[5,6]

Diagnostic Tests and Labs

Referral to an audiology specialist for audiologic assessment is essential for children diagnosed with Cockayne syndrome. Hearing tests may involve the following tone/behavioral audiometry and brainstem auditory evoked potentials.[7] Patients may require one or more of the following assessments:

- **Pure tone audiometry.** Audiologists measure pure tones of various frequencies via air (earphones) and bone (oscillator) conduction. Hearing loss appears to be greatest at the highest frequencies.[6]
- **Otoacoustic emission (OAE).** This type of hearing test measures the presence and strength of low-intensity sound produced by the cochlea in response to acoustic stimuli.
- **Auditory brainstem response (ABR/BAER).** This evoked electrophysiology test measures the way that the brainstem responds to auditory stimuli (clicks and tone bursts).[7]
- **Tympanometry.** This test measures changes in the acoustic resistance of the eardrum and middle ear in response to changes in air pressure.

Management

Hearing aids are a common management approach for children with Cockayne syndrome who are identified with mild to moderate hearing loss. Children with more severe hearing loss may be candidates for cochlear implants. Case studies of children with Cockayne syndrome type I who received cochlear implants demonstrated early improvements in hearing function, speech perception, and language ability.[6] Selection for cochlear implantation is determined on a case-by-case basis, and multidisciplinary care coordination is required between the patient and their families/caregivers, implant audiologist, and other members of the Cockayne syndrome care team.

Monitoring

Referrals to otolaryngology, speech-language pathology, and early intervention programs are recommended for children with Cockayne syndrome.[8] Early intervention programs, which often have different names in different states in the United States, allow children under 3 years of age with certain developmental issues to qualify for services. As the prevalence of vision problems is high among children with sensorineural hearing loss, formal ophthalmologic evaluation is also recommended. Audiologic evaluation is recommended at least annually.[9]

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Cardiology

Cardiovascular Complications

Overview

Cockayne syndrome is clinically characterized by many features of aging, including atherosclerosis, intima medial thickening, and vasculopathy. Many CS patients develop stroke, mild to moderate or accelerated hypertension, and other forms of cardiac dysfunction (eg, systolic murmur, aortic root dilatation, cardiomyopathy).[1-4] A recent retrospective cohort analysis (n=21) reported that 71% of CS patients had elevated blood pressure; although, it is important to note that hypertension in CS patients is often renal in origin.[2] A recent case study reported an association of moyamoya vasculopathy and CS that presented as cerebral ischemia.[5]

Management Considerations

Poor peripheral circulation is a common feature in a majority of CS patients, resulting in cold extremities.[6,7] Poor circulation often complicates venous access. In order to minimize distress of repeated attempts at venipuncture, experienced staff should be involved in establishing venous access in CS patients whenever possible. Clinicians might consider evaluation for cerebral ischemia in patients who present with episodes of focal weakness or focal seizures.[5] A neurologist should be consulted about the advisability of evaluations such as electroencephalography (EEG) and magnetic resonance imaging (MRI).

Assessment and Monitoring

Assessment of liver and renal function, blood pressure, and blood glucose are recommended in CS patients at least once annually, perhaps twice annually depending on the patient's overall health status. A consultation with a cardiologist regarding the advisability of evaluations such as electrocardiography (ECG) and echocardiography may be prudent in patients with clinical symptoms of cardiovascular disease.[6]

Respiratory Complications

Respiratory complications, such as infections (75%), restrictive lung disease (15%), and asthma (10%), have been reported in CS patients,[6] and pneumonia has been reported as a cause of death.[8] Aspiration is an identified cause of recurrent infections; therefore, clinicians should refer patients with recurrent respiratory infection to a pulmonologist for overall respiratory care and to a speech pathologist for swallowing assessment.

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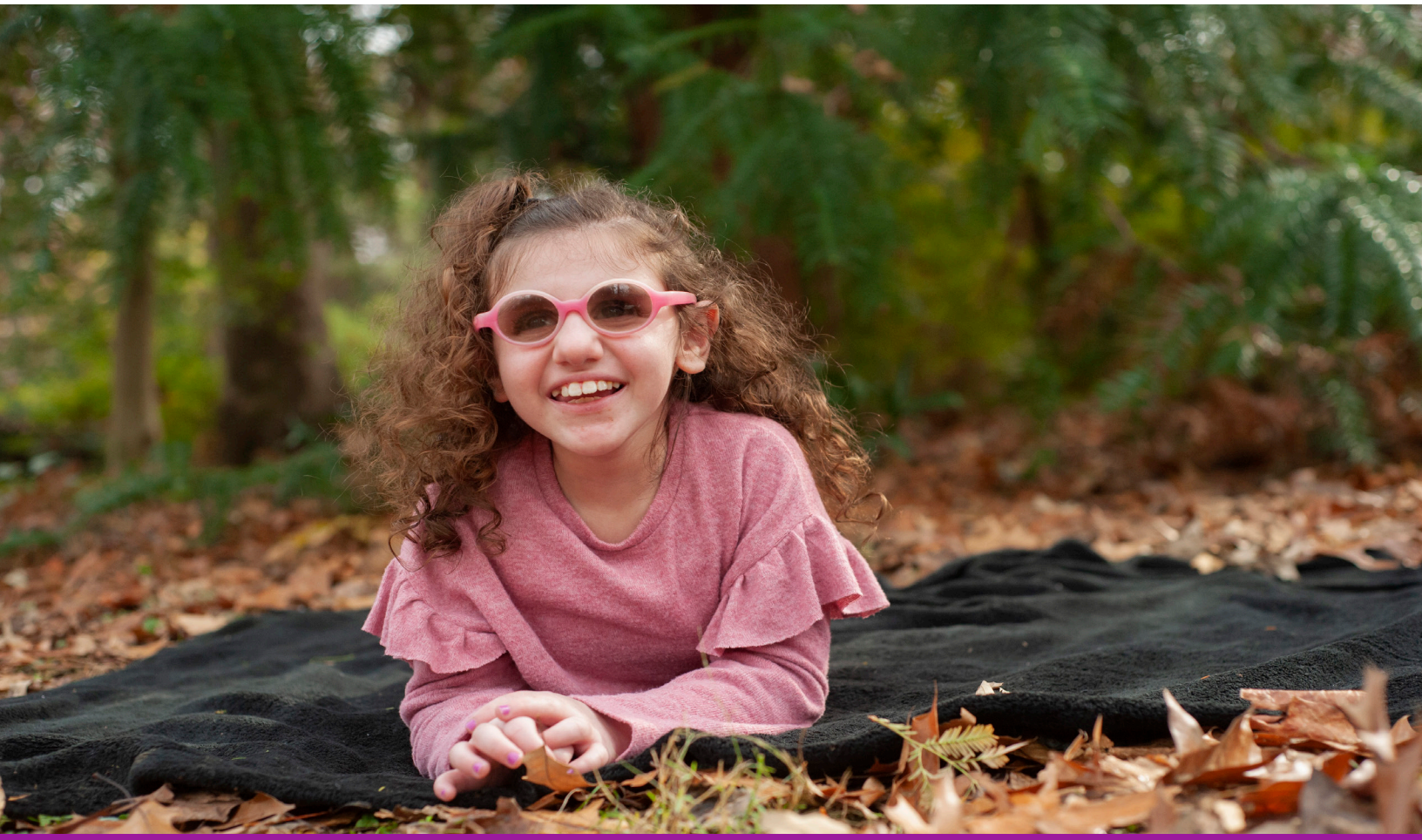

Dental and Oral Care

Overview

Dental anomalies are a characteristic feature of Cockayne syndrome.[1-3] The presence of dental caries is considered one of the minor diagnostic criteria.[4]

Signs and Symptoms

Case report data indicate several anomalies in the size, shape, number, and structure of teeth occur in patients with Cockayne syndrome. Enamel hypoplasia is a common anomaly in most patients. Other observed anomalies include tooth malposition, shovel-shaped upper central incisors, delayed eruption of primary teeth, and absence of permanent teeth (hypodontia).[3] Hypodontia is associated with several subsequent dental problems, including abnormal spacing of teeth and delayed tooth formation.[5]

Although dental caries are not specific to Cockayne syndrome, they are observed in approximately 50% to 75% of patients with Cockayne syndrome.[3] Several features contribute to dental caries in Cockayne syndrome, including preexisting enamel hypoplasia, decreased salivation, poor oral hygiene as a consequence of neurological impairment, gastroesophageal reflux, and vomiting.[3] Some patients may also have a high arched palate.[4]

Evaluation and Management

It is important to distinguish normal from pathologic dental development in children with Cockayne syndrome through ongoing, regular evaluation. Clinicians should encourage caregivers to maintain a regular dental evaluation schedule for early identification of abnormalities.[1] Similarly, although caries occur in children with CS despite oral care and tooth brushing, clinicians should advise caregivers to continue assiduous oral care as recommended by the American Dental Association, brushing twice per day.

The first dental evaluation should occur when the first tooth erupts to identify obvious defects or malformations.[6] The parent should be shown how to clean the child's teeth at that stage of development and encouraged to make it a a daily habit. If need be, the child can lie across the laps of parents sitting knee-to-knee, with the head in the lap of one adult. With parental persistence, the child can be desensitized. This is a necessity if the child resists good oral hygiene. The child may never be able to perform optimal oral hygiene alone. Dental considerations for the patient with congenital craniofacial defects range from routine care to treatment of the malformation. If the child with congenital defects is also intellectually challenged, the child could be difficult to treat.[6]

Complete dental evaluation is warranted for children in whom tooth eruption is delayed more than six months beyond the normal age range for a particular tooth. Radiographic evaluation is usually required to visualize the bone and teeth structure of children with dental abnormalities. Dental

abnormalities typically require treatment in the first few years of life. Dental extraction may be required for abnormalities.

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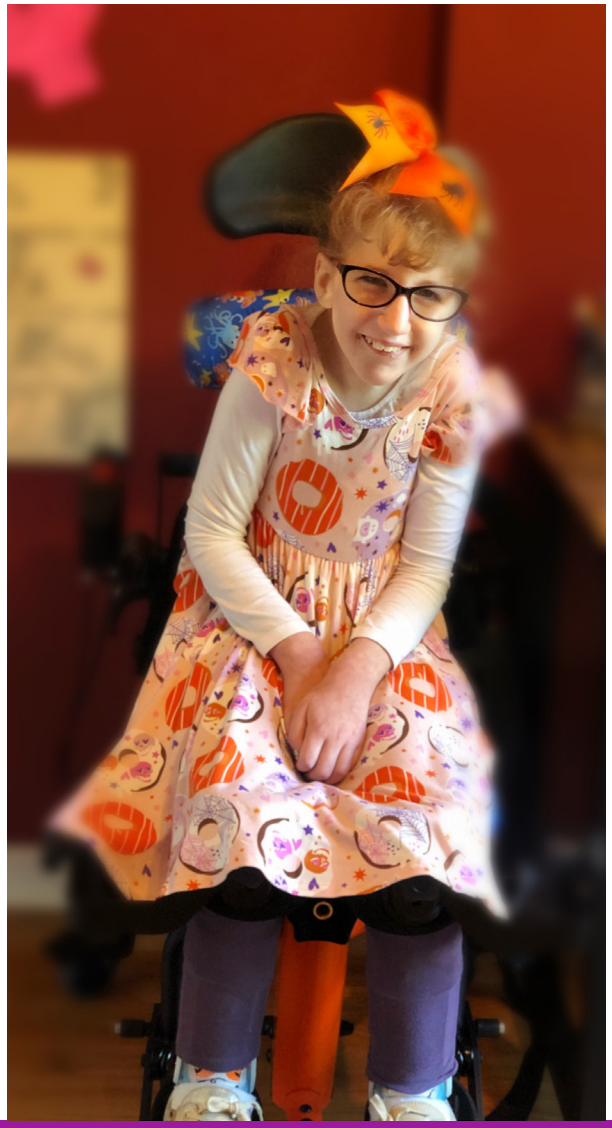

Dermatology

Overview

Cutaneous manifestations are common in nucleotide excision repair disorders such as Cockayne syndrome. Photosensitivity has been identified as a cardinal symptom of CS, present in approximately 75% to 96% of patients.[1,2] Other CS dermatologic findings include photosensitive dermatitis (dry skin, erythema, scale), hyperpigmentation, atrophy, telangiectasia, cyanotic acral edema of extremities, nail dystrophies, and hair anomalies. Acral edema is also a dermatologic finding in CS patients, contributing to vascular complications such as cold and edematous feet.[3] As CS patients grow older, the fat surrounding the eyes decreases, leading to sunken eyes.[2] The skin around the temporal areas and eyes can become progressively thinner, and veins become more visible.[3] Exaggerated hair loss has been reported in approximately 5% of CS patients, and nails can be affected by abnormal longitudinal curvature (clubbing), abnormal growth, and distal onycholysis.[3]

Photosensitivity

CS children often develop photosensitivity in early childhood (even before one year of age).[2] Sun exposure is characteristically followed by facial erythema in a butterfly distribution.[4] Sensitivity to UV light in CS is often acute and contributes to sun damage. Although sun-exposed skin in CS patients may be prone to lesions, photosensitivity in CS has not yet been linked to sun-induced neoplasms.[3] The lack of association of CS with sun-induced pigmentation is a key differentiator of CS from xeroderma pigmentosa.[3]

Evaluation and Management

Strict sunlight avoidance and protective measures, such as staying in the shade and wearing protective clothing (eg, wide-brimmed hats, long-sleeved shirts), are vital for CS patients. Broad-spectrum chemical sunscreen agents absorb damaging radiation and provide both UVA and UVB protection. Clinicians should advise parents of CS children to liberally apply an SPF 30 sunscreen every 2 hours if outdoors.[4] A dermatologist should conduct a full skin evaluation of children with CS on an annual basis.

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Emergency Medicine

Overview

Patients with Cockayne syndrome may require emergency care for disease complications. Emergency medicine and critical care clinicians, as well as internists and primary care physicians, should be aware of medications to avoid and refer patients for specialist management, particularly when patients present with acute or rapidly progressive complications. Patients that are fed via nasogastric or percutaneous endoscopic gastrostomy (PEG) tubes may not be able to communicate abdominal pain associated with some inflammatory gastrointestinal conditions, such as pancreatitis.

Medications to Avoid

Metronidazole

Metronidazole (also known as Flagyl®) is absolutely contraindicated for CS patients, meaning they should never receive this medication under any circumstances. Loose stools with or without constipation are common in CS and can affect up to one-third of patients.[1] Although metronidazole, a synthetic nitroimidazole antibiotic, is commonly used preemptively to treat anaerobic gut infections and manage patients in the general population with new-onset diarrhea or other manifestations of gastrointestinal dysfunction, physicians and other health care professionals should be aware that metronidazole can cause acute liver failure in CS patients.[1] While rare (affecting approximately 8% of CS patients), presentation of metronidazole toxicity may include signs and symptoms associated with paracetamol (acetaminophen) toxicity, including jaundice and steatorrhea.

Metronidazole toxicity is associated with the following clinical features:[1]

- Elevated liver transaminase levels
- Blood clotting (coagulation) abnormalities
- Neurotoxicity

Ideally, other nitroimidazoles should be avoided. However, if they are administered, clinicians should do so with extreme caution and closely monitor liver function and coagulation laboratory values for two to four weeks following the last administration.[2]

Opioids and Sedatives

Use of opioids and sedatives is not recommended in CS patients.[3] Case reports have described exaggerated responses, such as respiratory depression and blunted affect, to sedative and opioid medications (eg, codeine).[2]

Endocrine and Metabolism Complications

- Abnormal glucose metabolism (eg, hypoglycemia, impaired glucose tolerance, insulin resistance and diabetes) is present in approximately 13% of CS patients older than 16 years.[2] Nasogastric or PEG tube feeding can also complicate

existing diabetes due to the 24-hour cycle of calorie intake. Patients on such schedules may require insulin administration.

- Patients have been reported to need high insulin doses and even insulin-sensitizing agents such as thiazolidinediones to combat insulin resistance.[4-5] Triglycerides can be significantly elevated in these patients and need to be monitored to evaluate for the risk of pancreatitis.
- Emergency medicine physicians, critical care specialists, and other clinicians should also be aware that the risk for overfeeding and fluid overload is high in CS patients, potentially leading to hypervolemia and disruption of homeostasis.[6] Fluid resuscitation should be conducted carefully in situations where acute dehydration exists.
- Clinicians should refer CS patients with endocrine and/or metabolic concerns to an endocrinologist for specialist management.

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Endocrinology

Overview

A range of endocrine abnormalities has been reported in Cockayne syndrome, including hypogonadism, delayed/absent sexual maturation, hypothyroidism, and diabetes.[1,2]

Sexual Maturation

Although most CS children will develop secondary sexual characteristics, hypogonadism is prevalent and suspected to be hypothalamic in origin.[3] Approximately one-third of boys with CS will have undescended testes, and menstruation is often characterized by irregular cycles.[3]

Hypothyroidism

Patients with CS may be at an increased risk for hypothyroidism. In the Cockayne Syndrome Natural History study, 8 out of 102 patients presented with hypothyroidism.[4] Thus, screening for this condition may be appropriate, especially because symptoms can be difficult to ascertain in this patient population.

Endocrine and Metabolic Complications

Abnormal glucose metabolism and associated conditions (eg, hypoglycemia, impaired glucose tolerance, insulin resistance, and type 2 diabetes mellitus) are present in approximately 13% of CS patients older than 16 years.[4] Hyperinsulinemia has also been reported.[2,3] A 2019 case report described a rare case of a normal-weight patient with CS who presented to the emergency department with new-onset severe insulin-resistant diabetes mellitus, suggesting the need for further investigation of the association between CS and insulin resistance.[5] Nasogastric or PEG tube feeding can also complicate existing diabetes due to the 24-hour cycle of calorie intake, and patients on such schedules may require insulin administration. Patients have been reported to need high insulin doses and even insulin-sensitizing agents, such as thiazolidinediones to combat this insulin resistance.[3,4] The management of diabetes in CS patients can be complex and warrants specialist oversight from an endocrinologist. Triglyceride levels can also be significantly elevated in these patients, likely in relation to the insulin-resistant state, and need to be monitored, as they may present an increased risk for pancreatitis.

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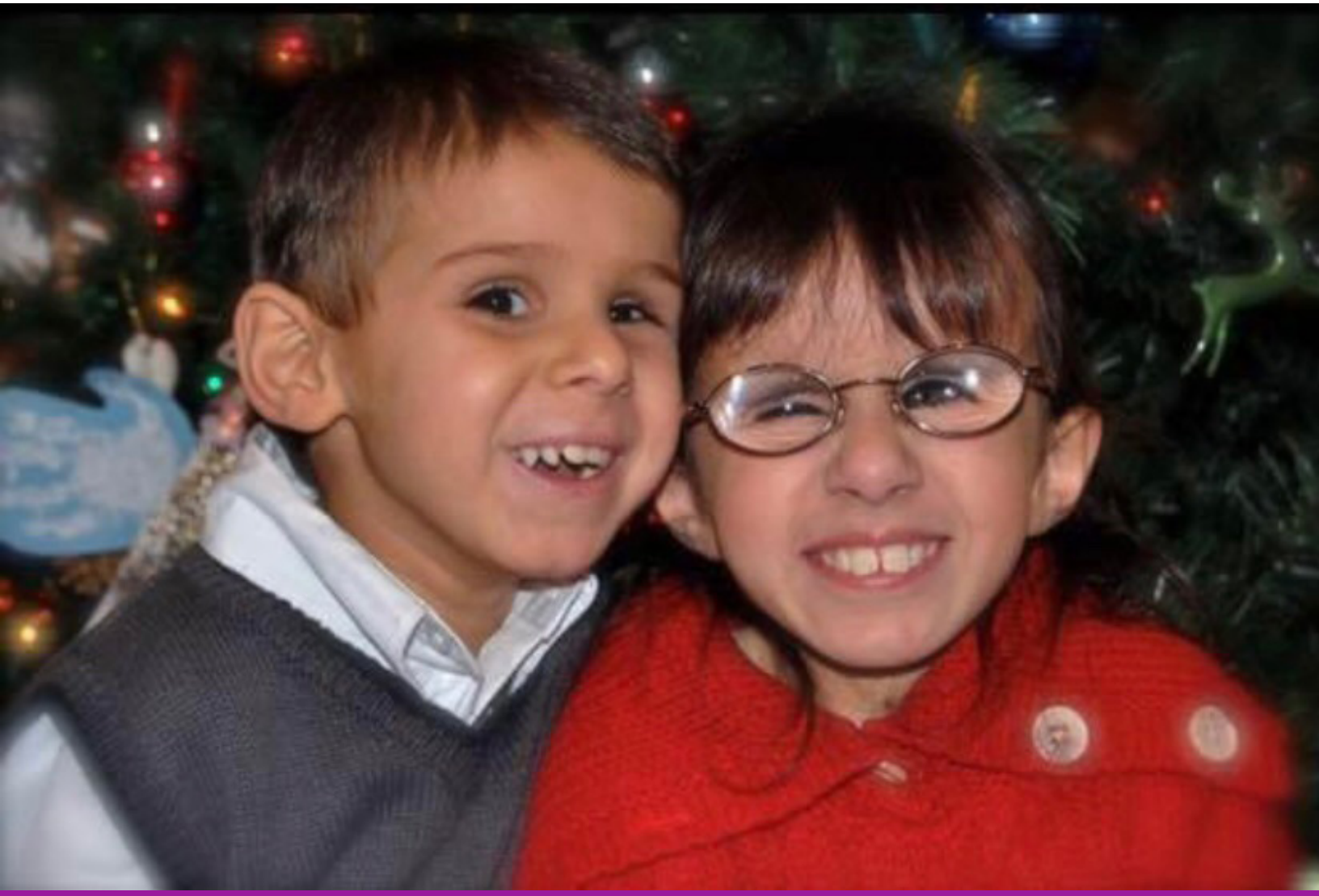

Gastroenterology and Nutrition

Weight and Nutritional Status

Weight in CS children tends to be low, and nutritional status is often poor. Oral intake can be challenging for these children due to accelerated muscle wasting,[1] and many patients also have severe gastroesophageal reflux disease (GERD), which may exacerbate weight loss.[2] Increased gastrointestinal motility is often present in CS as well as hepatomegaly or splenomegaly on physical examination and elevated plasma levels of transaminases, which are mostly asymptomatic.[1,3] Annual physical examination and liver enzyme testing are recommended. Increased metabolism offers one explanation for weight loss, but it is also important to note that children with CS do not appear to have the caloric needs expected for body size or age.[4]

Measuring Growth

Prior to a diagnosis of CS, slow growth can give rise for concern about the adequacy of dietary intake. However, following diagnosis, clinical status rather than growth should be the primary factor guiding clinical decision-making about nutrition management. Clinicians can consider initiating a growth chart to measure and plot growth,[5] monitor body mass index, and evaluate resting energy expenditure to determine caloric needs.[4]

Managing Nutrition

If children with CS have intact oral function, feeding therapy under the guidance of an occupational or speech therapist can help to improve coordination or sensory-related feeding issues. However, many children require supplementary nasogastric or PEG feeding to manage poor growth or weight loss. As many as two-thirds of children who initially require nasogastric feeding may transition to PEG feeding.[2] Jejunal tubes offer an alternative percutaneous approach that may alleviate vomiting and reflux associated with GERD and also allow medication administration.[4]

Subcutaneous fat loss is a common feature among CS children and can lead to stomach contents leaking from the percutaneous tube insert, further reducing calorie intake and leading to skin irritation. Although feed volumes can be moderately increased to support weight gain, clinicians should be aware that the stomachs of children with CS may be unable to accommodate increases in feeding volume.[2] It is critical to avoid overfeeding and fluid overload, which can disturb homeostasis and lead to hypervolemia.[6]

Attention to the caloric requirements for CS is key, and it is important to evaluate resting energy expenditure to determine the caloric needs for CS patients.[4] A high-fat diet developed in consultation with a dietician may attenuate the high metabolic rate that is a feature of CS in some patients.[1] If it is unclear whether weight loss is due to inadequate intake or to pathological subcutaneous fat loss, consider titrating nasogastric/PEG feeds against

weight gain, and avoid rapid increases in feed volume.[2,5] Diabetes and abnormal blood glucose metabolism are common complications in CS.[2] Therefore, clinicians should monitor body mass index and annually assess blood glucose levels.[5]

Other Considerations

- Nutrition imbalance can also lead to constipation and/or loose stools, which may cause diaper rash. Early management of diaper rash is key to preserve skin integrity.[2]
- It is imperative to avoid administering metronidazole (also known as Flagyl®) to CS patients who might seek emergency department management for loose stools or other manifestations of gastrointestinal infection. Metronidazole has been shown to cause acute liver failure in CS patients and is contraindicated in this patient population.[7]
- Proton pump inhibitors can be used to manage GERD either alone in absence of a suitable and approved prokinetic agent or an H2-recceptor antagonist.[2] Fundoplication may also be required.

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Genetics

Genetic Causes of Cockayne Syndrome

The two classic Cockayne syndrome genes are the *ERCC8* (excision repair cross-complementing, group 8) gene, which encodes CSA and accounts for about 20% of cases, and the *ERCC6* gene, which encodes CSB and is causative in the majority of cases.[1,2] Some patients presenting with CS harbor mutations in one of several xeroderma pigmentosum genes. These include *XPA* (encodes XPA), *ERCC3* (XPB), *ERCC2* (XPD), *ERCC4* (XPF), and *ERCC5* (XPG).[3-7] While all patients with xeroderma pigmentosum will characteristically display extreme photosensitivity, only a subset will also present with a CS phenotype and are classified as XP-CS.[8,9] In rare cases, CSB or XPD mutations result in cerebro-oculo-facial-skeletal syndrome (COFS), which shares several characteristics of CS type II.[2]

The molecular basis of CS does not systematically map to clinical phenotypes.[2] The common thread linking all of these genes is the involvement of their protein products in various aspects of DNA repair mechanisms. While in general, the CS phenotypes observed in patients are thought to be related to an underlying deficiency in the ability to repair mutations in DNA, researchers are exploring other possible roles for these proteins that may guide the development of future therapies.

Signs and Symptoms

As discussed in the Overview, general growth delay, delayed motor skill development, dwarfism, microcephaly, feeding difficulties, and sensitivity to sunlight are examples of potential initial clinical observations made by families and their pediatricians that cause them to seek input from genetics specialists. Differential diagnosis includes congenital abnormalities of the face, limbs, heart, or viscera; recurrent infections other than otitis media or respiratory infections; metabolic or neurologic crises; hematologic abnormalities; and cancer.[10] Growth failure is also seen in chromosomal, metabolic, endocrine, and gastrointestinal disorders.

Genomic and Laboratory Testing

CS diagnosis is based on identification of biallelic pathogenic variants in *ERCC6* or *ERCC8* via molecular genetic testing. Gene-targeted testing via a multigene panel that includes deletion/duplication analysis is recommended when phenotype findings suggest Cockayne syndrome.[10] DNA repair assays offer a diagnostic adjunct if molecular testing does not identify pathogenic variants in a CS-associated gene in patients suspect of having CS.

Recommendations for Follow-up

Once a genetic diagnosis is established, it is important to closely

monitor patients diagnosed with CS for complications and to identify management needs. While some geneticists will continue to follow patients on an ongoing basis in collaboration with other medical specialists, others may defer ongoing management to other specialists, such as neurologists, dermatologists, gastroenterologists, and ophthalmologists (Table 2).

Genetic Counseling

Genetic counseling is recommended as a basis for information about the nature, inheritance, and implications of CS to clarify genetic status for family members and support decision-making. Genetic counseling can review available genetic information with individuals as a basis for discussing inherited risk, clarifying carrier detection status, and determining options for family planning. Prenatal testing and preimplantation diagnosis are options for pregnancies at risk for CS.[10]

Table 2. Recommended Evaluation Parameters Following Diagnosis*

System	Evaluation
Growth	• Growth chart measurement and charting • Feeding assessment
Development	• Developmental assessment » Motor, adaptive, cognitive, speech/language needs » Early intervention/special education needs
Neurologic	• Brain MRI • Muscle tone, contracture assessment
Ophthalmologic	• Ophthalmologic assessment
Ear, nose, and throat	• Audiology assessment
Dental	• Dental evaluation
Dermatologic	• Skin assessment
Skeletal	• X-ray if warranted to document skeletal dysplasia
Renal	• Renal function tests
Hepatic	• Hepatic function tests
Other	• Genetic counseling

*Adapted fromLaugel V. Cockayne Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*®. University of Washington, Seattle; 2019.[10]

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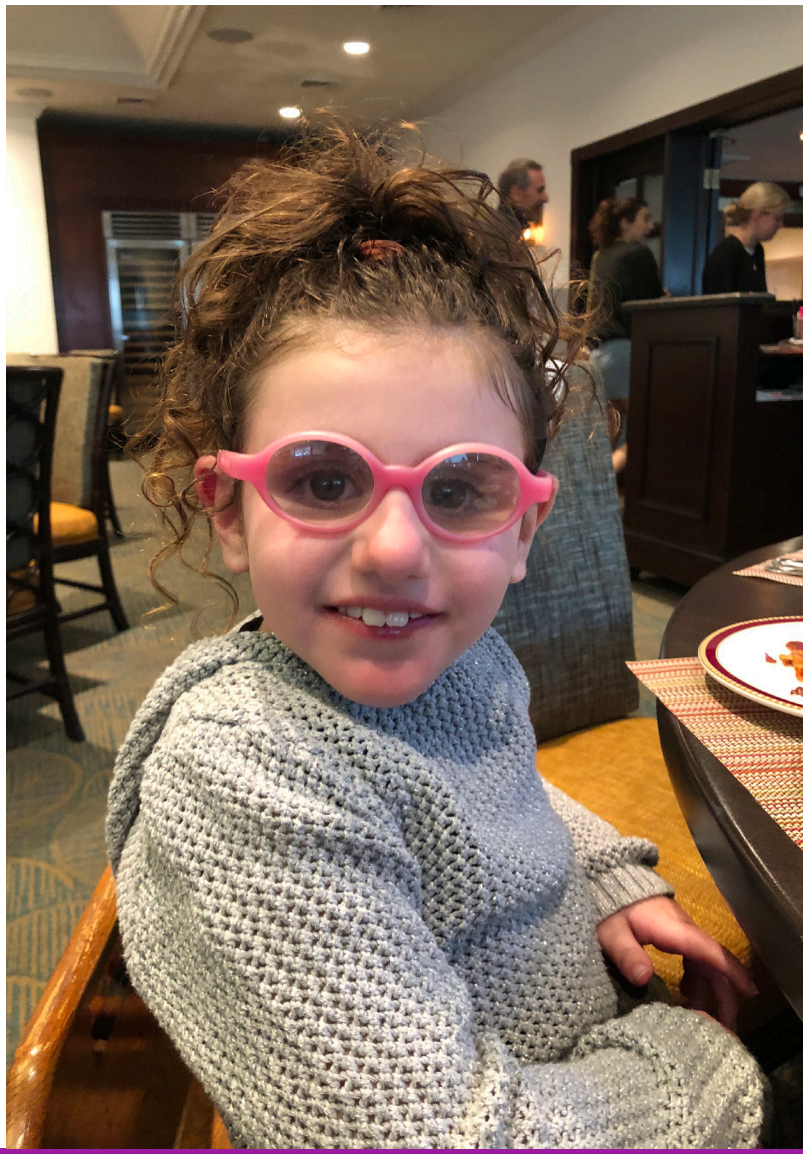

Nephrology

Renal Complications

The prevalence of renal complications is high in children with Cockayne syndrome.[1] Although the precise mechanisms of renal impairment are unclear, it is hypothesized that the accelerated aging process plays a role. Premature onset of atherosclerosis and hypertension in Cockayne syndrome can lead to renal complications, such as nephrotic proteinuria, elevated creatinine, hyperuricemia, and chronic kidney disease (CKD) as well as strokes and cardiac dysfunction.[1-3] Although there are limited data describing renal pathophysiology, nephron reduction, arteriolosclerosis, and glomerular hyalinosis are associated with Cockayne syndrome.[1] Anatomical renal abnormalities might also be present, such as unilateral or hypoplastic kidneys. Renal failure is a significant complication that requires close monitoring and treatment.[2]

Surveillance

Annual assessment of renal function, uric acid levels, and urinalysis is considered prudent, with more frequent monitoring needed if symptoms or laboratory abnormalities arise.[4] Children with Cockayne syndrome have decreased muscle mass; therefore, it is possible that normal levels of serum creatinine (which is derived from skeletal muscle) may be present in the setting of CKD in these patients. A small, longitudinal case series suggested that serum creatinine corrected for height might be useful in evaluating renal function in patients with Cockayne syndrome.[5] It may also be helpful to assess serum creatinine levels in the context of individual patients' baseline levels rather than relying solely on the reference ranges for a particular clinical laboratory. Periodic urinalysis screening is also warranted, as a high prevalence of proteinuria, which contributes to worsening of renal function, has been reported in cohort studies.[1,2,6] Uric acid levels rise with declining glomerular filtration rate (GFR) and can lead to hypertension, and hyperuricemia, which is an independent risk factor for more rapid progression of CKD.[1,7] Hypertension is also likely underdiagnosed in patients with Cockayne syndrome. Children with Cockayne syndrome are generally shorter in height than the general pediatric population (lower than the 5th percentile), and the threshold for hypertension is lower.[1] Therefore, blood pressure should be frequently assessed with appropriately sized cuffs. Monitoring for cardiac complications of hypertension such as left ventricular hypertrophy may also be appropriate.

Management

Renal dysfunction is one of several potential multisystem disorders in this condition, resulting in poor quality of life and reduced life expectancy. The following therapies can be considered in appropriate patients:

- Angiotensin-converting enzyme (ACE) inhibitors may slow

progression of renal disease in some patients.

- Anti-uric acid medications may be appropriate for patients with high uric acid levels.

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Neurology

Clinical Neurological Complications

Cockayne syndrome is a neurodegenerative disease that is accompanied by several serious neurological complications. Functional neurological complications can include motor and language delays, increased muscle tone, and tremors. Patients frequently experience increased tone and tremors,[1] and some patients develop epileptic seizures.[1,2] Neuropathies are typically divided into demyelinating and axonal categories; the former involves the fatty insulation around nerve fibers, while the latter involves the nerve fibers (axons) themselves. Demyelinating neuropathy is common and may be detected with nerve conduction studies and electromyography (EMG), whereas axonal neuropathy is relatively infrequent.[3] Peripheral neuropathy can lead to neurogenic bladder, muscle atrophy, hyporeflexia or areflexia, and locomotion disturbances.[4]

Neuroanatomical Complications

Anatomically, brain atrophy, white matter abnormalities, and basal ganglia calcifications are frequently seen on neuroimaging studies, such as brain MRI and computed tomography (CT).

Diagnostic Laboratory Tests

- When new neurological complications occur or are suspected, it is important for a neurologist to be consulted for guidance regarding the advisability of the various evaluations available.
- EEG studies do not need to be performed routinely, as epileptic seizures occur in a minority of patients with CS. However, unexplained spells of altered consciousness or rhythmic movements may require EEG evaluation. There are two general types of EEGs: routine and prolonged. The neurologist can work with the family to determine which type would have the greatest therapeutic utility for a particular situation.
- Nerve conduction studies and EMG tests might be indicated if patients experience symptoms concerning for peripheral neuropathy or for routine surveillance.
- Periodic brain MRI is helpful to identify and monitor the progression of brain atrophy and abnormal myelin. Calcification may also be seen. Many CS patients will need sedation in order to undergo these studies; thus, decisions on when to perform neuroimaging studies should

be based on individual patient considerations.

- Cranial CT scans are helpful for identifying brain calcifications and, to a lesser extent, brain atrophy. CT scans expose patients to radiation and thus may not be ideal for following abnormalities over time but generally do not require sedation. Due to radiation exposure, decisions on when to perform neuroimaging studies should be based on individual patient considerations.
- Sleep studies are useful for identifying a wide range of sleep disorders, from restless legs syndrome to various types of sleep apnea.

Management Considerations

- CS patients should have a developmental assessment as early as possible following diagnosis and should be screened for neuropathy. A baseline brain MRI should be considered if one has not been performed already.
- If peripheral neuropathy is asymptomatic, no treatment is needed. Symptomatic peripheral neuropathy should be treated with appropriate supportive measures, such as physical therapy and, if pain is present, certain medications. Gabapentin could be considered for neuropathic pain but should be started at very low doses due to the side effect of somnolence.
- In some cases, tremors respond to low doses of carbidopa-levodopa.[5]
- If epileptic seizures are diagnosed, antiseizure medications should be initiated. A wide range of antiseizure medications is available; however, antiseizure medications that are metabolized primarily via the liver should be used with caution in light of the liver fragility experienced by some CS patients. Downward dosage adjustments should be considered depending on the status of the liver and kidneys in these patients.
- Education settings must be optimized for children with CS who are affected by learning delays and academic difficulties. Individualized educational plans (IEPs) should be used whenever applicable to determine resources that can optimize the learning environment. It is important for any corrective lenses and hearing aids that are prescribed to be used in school to optimize educational opportunities

Recommendations for Follow-up

Patients with CS should see a neurologist at least annually, preferably twice a year, and more often if there are active complications or changes in

neurological status. Patients on medications such as carbidopa-levodopa or antiseizure medications should be seen by a neurologist at least twice a year to assess response and side effects.

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Ophthalmology

Signs and Symptoms

Corneal opacification and cataracts are common in approximately half of patients with Cockayne syndrome and are considered an important prognostic factor.[1] Cataracts are typically bilateral, and most develop before the age of four years. Cataracts that occur before the age of three years are associated with the risk of earlier hearing loss and contractures.[1,2] Cataracts that occur at later ages may have milder prognostic implications.[3] Other ophthalmologic manifestations include optic atrophy as a result of optic nerve fiber degeneration,[4] strabismus, hyperopia, decreased lacrimation, and nystagmus.[5]

Retinitis pigmentosa is the most common form of retinal dystrophy and typically presents with a "salt and pepper" pattern.[6] Retinal dystrophy is progressive and considered a hallmark of Cockayne syndrome. This condition may co-occur with cataracts; although, cataract onset typically precedes retinal dystrophy. Retinal dystrophy is typically clinically significant in advanced stages of disease, but indications of disease may be apparent on electroretinogram (ERG) prior to clinical impairment.[7] Visual prognosis is poor. Other visual abnormalities that have been reported in children with Cockayne syndrome include miotic pupils, xerophthalmia (dry eyes), corneal ulcers, hyperopia (far sightedness), optic disc pallor, microphthalmos, and narrow palpebral fissures.[1,7]

Diagnostic Laboratory Tests

CS patients should have a baseline ophthalmology examination following diagnosis, with follow-up examinations at regular intervals. The presence and progression of night blindness, peripheral field defects, fundus lesions, and abnormal ERGs inform the diagnosis of retinitis pigmentosa/retinal dystrophy. Full-field ERG is the definitive test for retinitis pigmentosa/retinal dystrophy, but a decision to obtain this test should weigh benefits and risks, as many children require sedation for this test.

Management

Cataracts. Surgical removal of the crystalline lens and intraocular lens placement with or without capsulectomy may be warranted if cataracts cause vision impairment and photophobia.[8] If cataracts are removed, the child may need to wear contact lenses, glasses or a combination of both. Many CS children wear glasses from an early age.

Retinal dystrophy. There are currently no therapies that halt the progression of pigmentary retinopathies or restore vision. Light protection and vitamin therapy may help slow the degeneration process. Studies suggest that many pigmentary retinopathies are partially light-dependent; therefore, wearing dark glasses

outdoors can offer lens and retinal protection against light rays. Supplementation with vitamins A and E may offer some protection for photoreceptors; although, studies on such supplementation are inconclusive.[6] New therapies for retinal pigmentosa such as transplantation and device implantation are currently undergoing investigation.

Recommendations for Follow-Up

Detailed ophthalmic evaluations of children with Cockayne syndrome are recommended. Such evaluations should include annual eye examinations, preferably with dilated fundoscopy, until at least age four years.[1,7]

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Orthopedics and Physiatry

Motor Dysfunction and Musculoskeletal Challenges

Progressive neurodegeneration is a prominent feature of Cockayne syndrome accompanied by gross, fine, and oral motor dysfunctions that also have a substantive effect on daily activities. Motor dysfunction features include unsteady gait, ataxia, tremor, and dysarthric speech. Tremors are often intention tremors, and onset can be associated with developmental regression as children become less skilled in fine and motor domains.[1] Impairment of the cerebellum, basal ganglia, vision, and vestibular systems combined with peripheral neuropathy can lead to significant ataxia and impeded ambulation.[2] Neuropathy can also lead to neurogenic bladder. Additionally, white matter changes in the brain, denervation myopathy, osteopenia, and disuse atrophy contribute to musculoskeletal challenges that include contractures, kyphosis, scoliosis, stooped posture, and muscle wasting.[2-4] Sunken eyes due to subcutaneous and orbital tissue loss is a frequent musculoskeletal abnormality in Cockayne syndrome.[1] Oral function, including speech and swallowing, is often challenging in patients with Cockayne syndrome, leading to speech delay and deficits in language, communication, and nutrition.[1] Indeed, many affected children have speech impairments, and some are minimally verbal or nonverbal.[4]

Management

Gross motor dysfunction. Physical, occupational, and speech therapies are recommended. Physical therapy should be considered to optimize mobility, maintain ambulation, and slow the progression of orthopedic complications such as contractures, scoliosis, kyphosis, or hip dysplasia/dislocation.[5] Referral to appropriate specialists can help with managing muscle tone abnormalities such as spasticity and dystonia. Durable medical equipment and devices such as wheelchairs, walkers, orthotics, bath chairs, and adaptive strollers can offer valuable support.[5]

Fine motor dysfunction. Referral to occupational therapy is recommended. Occupational therapy can support adaptive function by designing strategies to maintain the fine motor skills required for activities of everyday living (eg, feeding, grooming, and dressing). Occupational therapy may also help with strategies to cope with chronic tremors.

Oral motor dysfunction. Patients should be referred to a speech language pathologist for swallowing assessment and evaluation of speech, cognitive abilities, and sensory impairments.[5] Patients may benefit from augmentative and alternative communication (AAC) tools, such as picture-exchange communication and voice-generating devices.

Pharmacologic/surgical therapies. Several neurological conditions in children result in gross motor dysfunction that are difficult to treat and manage. Therapies such as carbidopa-levodopa, anticholinergics, and botulinum toxin have been reported as potential therapies for managing dystonia-ataxia and easing tightness. Patients with tremor may respond to carbidopa-levodopa. Notably, a case-series described the beneficial effect of carbidopa-levodopa on quality of life in three adolescents (mean age 13 years) by improving ability to engage in daily activities, such as writing, dressing, eating, and drinking.[3] Surgical intervention with globus pallidus interna deep brain stimulation (GPi-DBS) has also been reported as evoking partial or transient responses in patients with Cockayne syndrome.[6] Botulinum toxin should be used with caution, as it may worsen dysfunction due to peripheral neuropathy.

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Emerging Therapies

Current Investigational Therapies

As reviewed in the relevant chapters, the presenting symptoms of Cockayne syndrome guide supportive system-specific management strategies. There are currently several ongoing studies to investigate different aspects of CS, including metabolism,[1] clinical and laboratory abnormalities,[2] and natural history of the disease via development of a patient registry (the Coordination of Rare Diseases at Sanford Health).[3] Table 3 summarizes recent and ongoing clinical trials in CS. One experimental therapy in Europe, [5,10,15,20-tetrakis(4-carboxyphenyl)-21H,23H-porphine]manganese(III) chloride (known as MnTBAP), currently has orphan drug status for neutralizing toxic reactive oxygen species (ROS) and reactive nitrogen species (RNS), which cause cell damage in CS patients.[4]

Preclinical Therapeutic Development

A variety of CS therapeutic approaches are being tested in preclinical settings. This section provides descriptions of several types of therapies currently under investigation for CS. While these emerging therapies have yet to be proven to be effective for CS patients, they represent the variety of approaches being taken to tackle this disorder at the molecular level and may one day prove to be synergistic through simultaneously addressing the

Table 3. Investigational Clinical Trials in Cockayne Syndrome

Study name	Status	Clinical Trials ID	Phase	Agent
A Phase 1/2 Crossover Study to Evaluate and Compare the Pharmacokinetics of a Single IV Dose of D-mannitol to Single and Multiple Escalating Doses of Liquid Oral ProdarsanTM in Patients with Cockayne Syndrome	Completed	NCT01142154	Phase 1,2	Prodarsan
Metabolic Study of Cockayne Syndrome	Recruiting	NCT03044210		
Examination of Clinical and Laboratory Abnormalities in Patients with Defective DNA Repair: Xeroderma Pigmentosum, Cockayne Syndrome, or Trichothiodystrophy	Recruiting	NCT00001813		
Coordination of Rare Diseases at Sanford	Recruiting	NCT01793168		
An Observational Study to Assess the Natural History Including Growth and Hearing in Patients with Cockayne Syndrome	Terminated	NCT00985413		

underlying genetic deficiency as well as downstream impacts upon other cellular functions.

Gene Therapy

Gene therapy has great potential to treat a variety of disorders caused by genetic mutations. There are two main forms of gene therapy: (1) gene replacement therapy, in which the general goal is to provide a healthy copy of a mutated gene, and (2) genome editing, a newer, ever-evolving technology where a specific mutation in the genome is targeted for editing in every cell, which will result in correction of the mutation. Currently, most gene therapies being translated into the clinical realm are gene replacement therapies. However, one research group has recently demonstrated successful genome editing of a specific *ERCC6* mutation (G643T) in CSB-deficient cells.[5] Since CS can be caused by a wide variety of underlying mutations located in more than one gene as opposed to a single uniform mutation throughout the CS population, the gene replacement approach is more likely to be the method that initially undergoes clinical translation. In this case, (for example) all patients with an *ERCC8* mutation would receive the same therapeutic regardless of the specific *ERCC8* underlying mutation.

A gene replacement therapy for CS would involve delivery of either of the two classic CS genes (*ERCC8* encoding for CSA or *ERCC6* encoding for CSB) or one of the XP-CS genes (eg, *ERCC5* encoding for XPG) to cells that would normally express that gene. The gene delivered will depend upon the specific causative gene for each individual being treated.

The development of such a therapy for CS involves prioritization of tissues to target based upon greatest potential benefits to health and quality of life, with neurological tissues representing a likely prime target. However, as CS has multisystemic consequences throughout the body, it would be beneficial for any CS gene delivery strategy to provide a global whole-body treatment.

Injected genes do not efficiently enter cells on their own. Therefore, the gene delivery process requires the use of delivery vehicles, wherein healthy gene copies are packaged to facilitate cell entry. Certain viruses can easily enter cells and travel to the cell nucleus where genes are housed. These viruses can be used as vehicles for gene delivery by removing the vast majority of natural viral genomic material and replacing it with a healthy copy of the gene that is needed.

Amongst the many gene delivery vehicles that exist, adeno-associated virus (AAV) stands out as a highly promising candidate for several reasons: (1) it is a relatively nonpathogenic virus with a blunted immune response (ie, we have all been exposed to AAV, but it does not cause sickness); (2) different serotypes or versions exist in nature and others are being engineered in laboratory settings that are designed to target specific subsets of tissues; (3) AAV used in gene therapy persists as an episome and rarely inserts into the human genome, so there is limited potential for disruption

of otherwise healthy genes; and (4) AAV-mediated gene delivery provides high level, long-term expression in non-dividing cells because it enters the nucleus and persists as a circular piece of DNA for many years—this can be diluted out in constantly dividing cells such as skin but is not an issue for heart, brain, skeletal muscle, and other tissues where cells do not frequently divide. Further increasing its safety profile, the AAV used in gene therapies cannot replicate on its own, as the viral genes necessary for replication have been completely removed and replaced with a promoter and the therapeutic gene.

A general consideration for all therapeutics is to establish a minimum effective dose (MED). The objective of an MED is to expose each patient to the least amount of a therapy necessary to achieve a successful treatment response and, in so doing, minimize potential side effects and reduce the price of these costly molecular therapies. All of this increases the likelihood of successful translation of a treatment strategy to the clinic. For gene therapy, the way to minimize the effective dose is to strategically consider all of the elements in the delivery vector's design to ultimately achieve strong expression levels wherever they are required throughout the body.

AAV serotypes are slightly different versions of the same virus. The various AAV serotypes each have capsids (outer shells or containers that hold genes to be delivered) with features on their surface that determine their abilities to enter specific cell types. Selection of an optimal serotype for CS would balance known cellular tropism or affinity to enter certain tissues with current clinical information from human clinical gene therapy trials. Based upon these considerations, AAV9 may be an optimal choice for CS gene therapy, as this is the serotype currently being used in the FDA-approved gene therapy onasemnogene abeparvovec-xioi (Zolgensema) for spinal muscular atrophy (SMA).

Another way to control gene expression is through promoter selection. Promoters are DNA sequences that recruit the necessary elements to enable gene expression. The genetic material delivered in gene therapies includes a promoter to drive expression of the healthy gene. Certain promoters are more specific to particular tissues while others provide comparatively ubiquitous expression regardless of tissue. Through selection of a specific promoter, expression can either be restricted to specific tissues or broadly occur throughout the body. Based upon the multisystemic nature of CS, a broadly expressive promoter is likely the optimal choice for these patients.

Gene replacement therapies can also be designed to minimize the effective dose through the use of a method called codon optimization. Codon optimization of a genetic sequence optimizes the efficiency by which the delivered gene is processed into a functional protein. This species-specific approach would ensure that the genetic sequence being delivered utilizes the most efficient codons for human translation.

Lastly, one must consider how to deliver the gene therapy to the patient. One option is to directly inject the gene therapy into affected tissues. When the area affected by a disease is contained to a localized region or tissue (such as the eye) this may be a good option. However, genes delivered in this manner are only able to reach a limited area surrounding the injection site. For conditions such as CS where the entire body is a therapeutic target, a broader distribution is needed. Thus, the gene delivery route most likely to be used for CS is systemic intravenous (IV) delivery that would circulate throughout the body and expose as many tissues as possible to the therapeutic.

With the development of any therapeutic, it is extremely important to consider patient safety. For gene therapies, there are two main concerns that exist. The first is an immune response to the specific AAV serotype or capsid being used as a result of patients having been previously exposed to that particular AAV. These individuals would essentially be vaccinated against the AAV (even though it never caused sickness), and this could result in the body destroying the therapy before it has a chance to do its job. The second concern is an immune response to the gene product (eg, CSA, CSB, etc). Depending upon a patient's particular mutation and whether it results in any protein, the body may identify newly expressed healthy CS protein as foreign material and raise an immune response against it. These scenarios are both manageable through preventive administration of immunosuppressive drugs (eg, rituximab or prednisone) just prior to gene delivery in patients.

While currently the development of gene therapies for CS remains at the preclinical stage, research groups are working to develop this methodology for both whole-body/neurological targeting and the treatment of retinal degeneration in CS.[6]

Dietary Intervention

Other approaches to ameliorate the effects of CS are dietary in nature. One involves the testing of a high-fat diet to increase acetyl-CoA production.[7] CS patients share many of the same neurodegenerative traits that are observed in mitochondrial disorders, and both CSB-deficient mice and human cells have displayed mitochondrial alterations; therefore, a treatment focused upon improved mitochondrial function may be beneficial in the context of CS. In a comparative analysis, the effect of a high-fat diet, caloric restriction, and resveratrol (a plant compound that acts as an antioxidant) supplementation were assessed in CSB-deficient mice and healthy controls. The results showed a remarkable rescue of the metabolic and cerebellar CS phenotypes in CSB-deficient mice that were fed a high-fat diet, suggesting that these or other approaches to increase NAD+ or acetyl-CoA levels may represent valid therapies for CS.

Along these same lines, another group has demonstrated that niacin supplementation (active ingredient nicotinamide) successfully prevented the skin rash typically observed in an XP-CS (*ERCC5* [XPG]) patient when

exposed to the sun.[8] However, as significant psychomotor delay persisted, the positive impact of niacin supplementation was apparently restricted to a dermatological response and suggests that the mechanism underpinning the impaired UV response in patients differs from that which causes oxidative stress and premature aging. Regardless, the results of this study suggest that niacin supplementation may represent a worthwhile preventive measure for those CS or XP-CS patients that develop UV sensitivity.

Antioxidant Treatments

Several research groups have shown that one of the many features of CS is mitochondrial dysfunction and that this ultimately leads to decreased energy production capabilities in patients. High levels of ROSs have been observed in cells from patients with CS as compared with patients with more mild mutations in *ERCC6* and *ERCC8* that result in UV-sensitive syndrome alone.[9] An interesting study using CS patient–derived cells has shown that CSB deficiency affects mitochondrial turnover.[10] The authors suggested that a novel pathway of CS dysfunction is deregulation of a serine protease due to high levels of ROSs and that this protease degrades mitochondrial DNA polymerase gamma (POLG1), which impairs mitochondrial function. Interestingly, exposure of the cells to MnTBAP (a synthetic metalloporphyrin that mimics superoxide dismutase and scavenges ROS and peroxynitrite) resulted in significant reduction of ROS and peroxynitrite in CS cells and an impressive increase in mitochondrial-derived ATP.

In sum, although the results of this study suggest that antioxidants may be beneficial in CS populations, the studies were performed in primary CS patient–derived fibroblasts and may be another example of a treatment approach where the benefit is restricted to dermal cells. Further work is needed to test antioxidants in other CS-impacted tissues.

Deep Brain Stimulation (DBS)

There has been one report of stimulation of the ventral intermediate nucleus of the thalamus in a single CS patient.[11] The investigators found a marked and progressive response to thalamic stimulation within weeks of the surgery, and the improvement in motor systems persisted into the fourth postoperative year. Although the results in this single patient study were promising, there is no report of this therapeutic approach being tested in other CS patients.

Organizations that Provide Support for Cockayne Syndrome

- **National Initiative for Cockayne Syndrome:** http://nics-online.org/
- **National Institutes of Health Genetic and Rare Disease Information Center:** https://rarediseases.info.nih.gov/diseases/6122/cockayne-syndrome
- **Amy and Friends:** https://www.amyandfriends.org/
- **National Organization for Rare Diseases:** https://rarediseases.org/rare-diseases/cockayne-syndrome/

- **Orphanet:** https://www.orpha.net/consor/cgi-bin/index.php
- **Metabolic Support UK:** https://www.metabolicsupportuk.org/
- **Share and Care Cockayne Syndrome Network:** http://cockaynesyndrome.org/

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Appendix. Medications Used to Treat Symptoms in Cockayne Syndrome

This table was created from the clinical experiences of children with Cockayne syndrome who were prescribed these medications. Much of the content in this chart is based on case studies and parent or caregiver reports. It should be noted that not all children will react to medications in the same manner.

The table is constructed to have the physician discuss the information regarding safety and dosing concerns with individual choice of medications.

Drug class	Medication	Used for/clinical indication	Known reactions
Anesthesia	Propofol	Sedative	Cases of extreme drops in blood pressure reported in CS children
	Vecuronium	General anesthesia	Not to be used in people with liver/kidney issues; a case report of severe drop in blood pressure reported
Angiotensin II receptor blockers (ARBs)	Losartan	Used to lower blood pressure and reduce the risk of stroke Also used to slow long term kidney damage in patients with type 2 diabetes	No adverse reactions reported

Drug class	Medication	Used for/clinical indication	Known reactions
Antibiotics	Azithromycin	Antibiotic	No adverse reactions reported
	Cephalexin	Antibiotic	Diarrhea and vomiting reported in one case
	Clarithromycin	Antibiotic Also used with other meds to treat stomach ulcers	No adverse reactions reported
	Doxycycline	Antibiotic	Can cause permanent yellowing or greying of teeth
	Metronidazole	Antibiotic	**AVOID!** Can be fatal
	Trimethoprim	Antibiotic	Diarrhea and vomiting reported
	Trimoxazole	Antibiotic	No adverse reactions reported
Anticonvulsants	Levetiracetam	Antiepileptic	No adverse reactions reported
Antidiarrheals	Loperamide	Motility agent, antidiarrheal agent	No adverse reactions reported
Antihistamines	Cetirizine	Antihistamine	No adverse reactions reported
Bile acid sequestrants	Cholestyramine	Cholesterol-lowering agent	No adverse reactions reported
Calcium channel blockers	Amlodipine	Antihypertensive, treatment for angina, and other conditions caused by coronary artery disease	No adverse reactions reported

Drug class	Medication	Used for/clinical indication	Known reactions
D2 receptor antagonist	Domperidone	Motility agent	Regular heart monitoring and ECG recording should be performed when prescribed this medication
Decarboxylase inhibitors	Carbidopa-levodopa	Used for movement disorders and tremors	No adverse reactions reported
Gabapentinoids	Gabapentin	Anti epileptic	No adverse reactions reported
Histamine H2-receptor antagonist	Ranitidine	Gastric acid blocker	No adverse reactions reported
Human B-type natriuretic peptide	Nesiritide	Antihypertensive **Afterload reducer for congestive heart failure**	No adverse reactions reported
Insulin	Insulin aspart or glargine	Antidiabetogenic	No adverse reactions reported
NSAID	Naproxen	Antiinflammatory	No adverse reactions reported

Drug class	Medication	Used for/clinical indication	Known reactions
Opioids	Paracetamol-codeine	Analgesic	Prescribing doses are to be used with caution; reactions noted of increased analgesia and nonresponsive children due to dosage
	Morphine	Analgesic	Prescribing doses are to be used with caution; reactions noted of increased analgesia and nonresponsive children due to dosage
	Tramadol, hydrocodone, and other opioids	Analgesic	To be used with extra vigilance; CS children recorded to have an exaggerated response, ranging from respiratory depression to blunted affect that can last several days
Proton-pump inhibitors	Omeprazole	Gastric acid blocker	No adverse reactions reported
	Lansoprazole	Gastric acid blocker	No adverse reactions reported
Sedatives			To be used with extra vigilance; children with CS have been reported to have issues keeping warm and taking longer to wake up from anesthetics

Drug class	Medication	Used for/clinical indication	Known reactions
Skeletal muscle relaxants	Baclofen	Used to treat muscle symptoms including spasm and stiffness	No adverse reactions reported
Supplements	Melatonin	Helps to regulate sleep, commonly prescribed to treat insomnia	No adverse reactions reported
Thyroid hormones	Levothyroxine	Used to treat hypothyroidism (low thyroid hormone). It is also used to treat or prevent goiter (enlarged thyroid gland), which can be caused by hormone imbalances, radiation treatment, surgery, or cancer	No adverse reactions reported
Tricyclic antidepressants	Amitriptyline	Antidepressant	No adverse reactions reported