To improve the quality of life through family support, research, and education.

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Cardio-Facio-Cutaneous Syndrome

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Caring, Facilitating & Connecting

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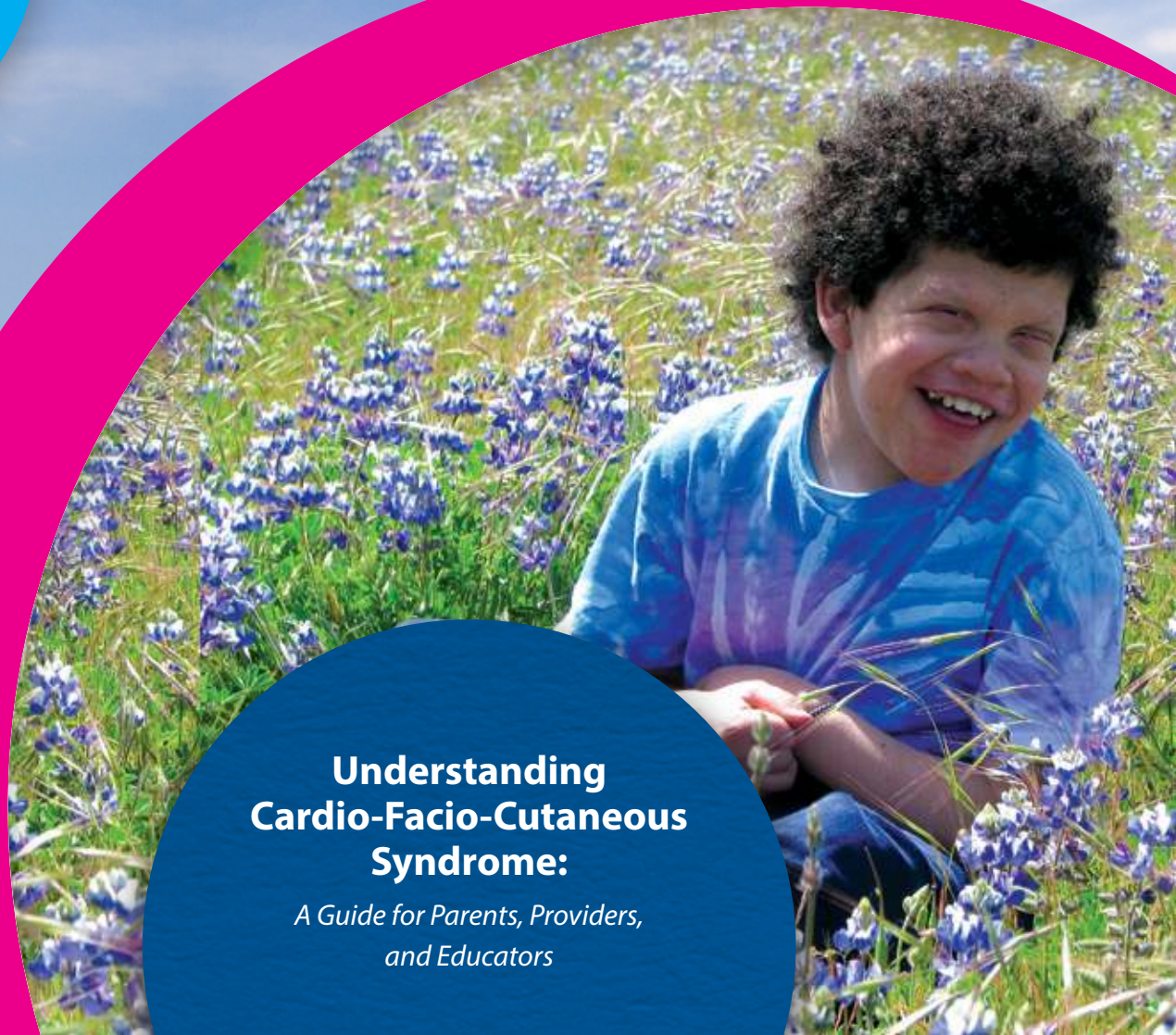

Understanding Cardio-Facio-Cutaneous Syndrome:

A Guide for Parents, Providers, and Educators

CFC International
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Introduction

Most likely you have never met someone who has Cardio-Facio-Cutaneous (CFC) syndrome. You are told that this is the reason your child has medical problems and/or physical differences. On the one hand, you may feel relief that your search for a diagnosis is over. On the other hand, you may feel overwhelmed by this news. It can be difficult to understand the information you are being given about CFC syndrome. This booklet is yours to be read at your own pace. As your child grows and develops, you'll probably refer to it often. In time, you will have the information you need to be the best possible parent to your child. Your interest in helping your child is obvious by your initiative to learn more and read this booklet.

Establishing a diagnosis can help parents, teachers, and doctors provide the best possible care for your child. Knowing a diagnosis can help you to anticipate possible future medical difficulties and developmental hurdles. In addition to a pediatrician, your child may need to see medical specialists such as: geneticists, cardiologists, neurologists, ophthalmologists, GI doctors, endocrinologists, orthopedists, and Ear, Nose, and Throat specialists. Therapies may include speech, physical, and occupational. Many children have a different lifestyle due to frequent visits to doctors and therapists. Early Intervention services can help children learn new skills. Many parents have found that most new skills are obtained through constant reinforcement. Some parents report very few developmental delays while others express concerns over prolonged feeding problems and language impairments. Receptive language skills are consistently higher than expressive skills. Although the children share a common thread, they all vary in their development, medical conditions, and individual needs.

In the following pages you will find information that will answer many of your questions concerning CFC syndrome. CFC International hopes this booklet helps you adjust to the diagnosis and dispel some of your fears.

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"Never doubt that a small group of thoughtful, committed people can change the world. Indeed, it is the only thing that ever has."

— MARGARET MEAD

This booklet is dedicated to all the families who have become part of our global family along with the doctors and researchers who continue to help us improve lives of those touched by CFC syndrome.

What is CFC Syndrome?

What is a syndrome?

The word syndrome is used to describe a cluster of features seen together and thought to have one underlying cause. Down syndrome is an example in which Dr. Down noticed that many people with intellectual disability had a similar appearance. Syndromes are caused either by mutations (changes) in our genes, environmental factors, or a combination of the two.

What is Cardio-Facio-Cutaneous syndrome?

This is a description of the physical findings in children with this syndrome. "Cardio" refers to the heart, "facio" refers to the face, and "cutaneous" refers to the skin.

How common is CFC syndrome?

Dr. Jim Reynolds and his colleagues first described CFC syndrome in 1986. It is a very rare condition with a few hundred cases reported in the medical literature, however, according to one study, CFC is thought to occur in approximately 1 in 800,000 individuals. The actual incidence is probably higher. CFC International keeps a registry of all individuals in the world with CFC syndrome in the hopes of reaching all families affected by this condition.

Findings in CFC syndrome

(Adapted from Online Mendelian Inheritance in Man)

There are often certain features that children with CFC share in common with one another. You may come across some of these terms in review of your child's medical records.

The head:

- Macrocephaly (relatively large head size)
- High forehead
- Bitemporal constriction (narrowed temples)
- Hypoplastic supraorbital ridges (some brow ridges which are underdeveloped)
- Sparse brittle hair

The face:

- Nystagmus (unsteadiness of the eyes)
- Downward slanting eyelid openings
- Sparse eyebrows
- Depressed nasal bridge
- Posterior angulated ears (ears tilted backward)
- Prominent ear helices (the outer rim of the ears appears large and fleshy)
- Ptosis (appears to have "droopy" eyes)

The chest:

- Pectus carinatum/excavatum (protrusion or indentation of the breastbone)

The hands:

- Predominant finger tip pads
- Thin, fast-growing, opal-colored nails

The skin:

- Generalized over-pigmentation
- Generalized ichthyosis-like dermatosis (scaly skin)
- Patchy hyperkeratosis (patches of thickened skin)
- Keratosis plantaris (thick skin on the sole of the foot)
- Keratosis pilaris (hair follicle prominence)

The heart:

- Pulmonic stenosis (narrowing of the valve in the pulmonary arteries)
- Atrial septal defect (abnormal opening between the left and right upper chambers of the heart-the tubes leading to the lungs)
- Hypertrophic cardiomyopathy (enlarged heart, thick heart muscle)

What causes CFC Syndrome?

CFC syndrome is caused by a mutation (change) in one of our genes. Genes are the bits of hereditary instructions that determine how we look and how our bodies develop and work. Everyone has about 25,000 pairs of genes. Our genes are located on structures called chromosomes that are found in every cell of our body. Chromosomes are inherited from our parents through the egg and sperm (one copy from our mother and one from our father). We look a little like both sides of our family because we inherit a copy of every gene from each parent. During conception, the egg and sperm fuse to form one cell with 23 pairs (total = 46) of chromosomes. The fertilized egg then duplicates over and over to form a baby.

Among the 25,000 genes in our bodies, there are at least four known genes that cause CFC syndrome. Individuals with CFC syndrome have one normal gene and one altered gene. The four genes found to be associated with CFC syndrome are called BRAF, MEK1, MEK2, and KRAS. Most individuals with CFC syndrome (75-80%) have a mutation in BRAF, with 10-15% having a mutation in MEK1 or MEK2 and <5% with a mutation in KRAS. Mutations in KRAS have also been identified in a few individuals with Noonan syndrome, therefore this may make it a little more difficult to interpret the results if an individual has a KRAS mutation. At this time we are still learning about the specific mutations in these genes and how they affect our children; however it is often difficult to predict the extent and severity of the condition in any given child.

CFC Syndrome and the RASopathies

CFC syndrome is one of several conditions that are caused by changes in genes in a metabolic pathway, called the Ras pathway. Two other conditions that are also caused by changes in genes in this pathway include Noonan syndrome and Costello syndrome. Noonan syndrome is much more common than CFC syndrome; however, Costello syndrome is very rare. Both of these conditions share many of the same physical and medical features in common with CFC, therefore, some children may have received one of these diagnoses first before getting the diagnosis of CFC syndrome. Even though these conditions are very similar to CFC, they also have differences that are important to recognize.

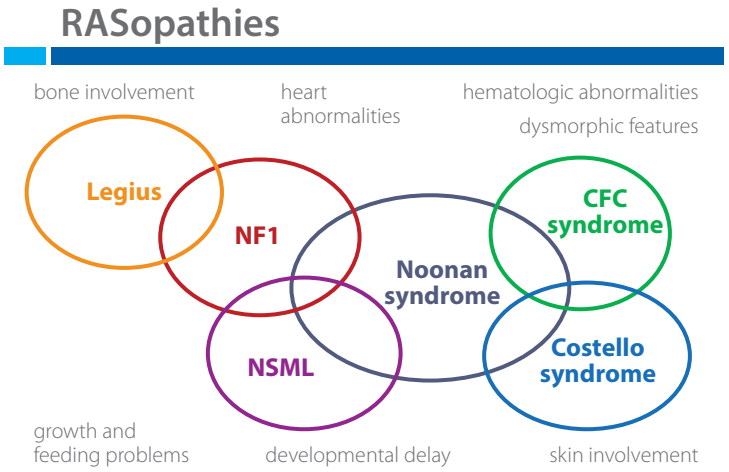

Image showing the similarities between RASopathy conditions.
Source: Pilar Magoulas, MS, CGC

Inheritance and Prenatal Testing

Is CFC syndrome inherited?

Nearly all cases of CFC syndrome to date have been sporadic, meaning that only one person in the family has CFC, therefore, the vast majority of cases of CFC are **not** inherited. However, there is one published report of an extended family with CFC syndrome where the change in the gene was passed on in several generations. CFC International is also aware of a family who has two children with CFC who were born to unaffected parents. This is likely caused by a rare genetic mechanism called gonadal (or germline) mosaicism, which happens when only the parent's egg or sperm cell is thought to carry the gene mutation.

If neither parent has CFC syndrome nor a mutation in one of the 4 genes, then the chance of having another child with CFC syndrome is very low (<1%). If, however, an individual has CFC syndrome, then there is a 50% chance of having a child with CFC syndrome.

Is prenatal testing available?

If you are considering having more children, you may be concerned that you will have another child with CFC syndrome. You should remember that the risk for unaffected parents of a CFC child to have another child similarly affected is very low. Or, perhaps your sister or brother is planning a family and is concerned. The risk your brother or sister may have an affected child is no greater than in the general population. Prenatal diagnosis is possible if the mutation in the individual with CFC syndrome is known. There are two different procedures that can be performed at different gestational ages. Chorionic Villus sampling (CVS) is a procedure that is performed between 10-14 weeks gestation and involves sampling some of the cells from the placenta and performing genetic testing on those cells. The risk of miscarriage from this procedure is thought to be <1%. The second procedure, called an amniocentesis, is performed between 16-20 weeks gestation and involves sampling cells found in the amniotic fluid. The risk of miscarriage related to amniocentesis is also very low.

Before making any decisions regarding prenatal diagnosis it is important to discuss the risks, benefits, and limitations with your healthcare provider or genetics professional. Some reassurance may be gained by a detailed ultrasound examination. This is a non-invasive procedure using sound waves to produce an image of the baby. Findings such as excess amniotic fluid (polyhydramnios) or a heart defect would be a clue to your doctors that this baby may have CFC syndrome. However, it is very important to remember that some babies without CFC syndrome also have these "nonspecific" findings. As a result, CFC syndrome may be suspected, but not diagnosed, during pregnancy. Conversely, some mildly affected CFC babies may not show particular changes on prenatal ultrasound.

Diagnosis of CFC Syndrome

How is someone diagnosed with CFC?

In the past, the diagnosis of CFC was based on the clinical features of the child. This means that a doctor recognizes several signs of CFC syndrome occurring together in an infant, child, or adult. Although a diagnosis may be possible in a newborn infant, most often the diagnosis is made in early childhood. With the discovery of genes associated with CFC syndrome, the clinical diagnosis is now able to be confirmed in those suspected of having CFC. Genetic testing of all four genes is clinically available in laboratories around the world. For a listing of laboratories that offer genetic testing for CFC syndrome, please visit www.genetests.org or contact your local genetics specialist.

Is there a Cure for CFC Syndrome?

Currently, there is no known cure for CFC syndrome. The genetic change responsible for CFC is in every cell of the body. At this time, there is no way to access every cell in the body to fix the gene mutation.

However, it is possible to treat many of the medical problems associated with CFC syndrome. Treatment should be based on the child's needs, rather than the diagnosis. For example, a child with a heart defect should be seen by a pediatric cardiologist and treated by that doctor as he or she would treat any child with the same heart defect.

MEDICAL MANAGEMENT AND RECOMMENDATIONS

The remainder of this booklet will review the most common medical, developmental, and behavioral findings in individuals with CFC syndrome, followed by a list of recommendations for management for each section. Please remember that every child is unique and your child will not likely have all of the findings listed in this booklet. This is meant to serve as a guideline for your child's health and management. A table summarizing the published healthcare guidelines and recommendations for management of CFC can be found on page 16.

In general, many of the following specialties will be involved in the care of individuals with CFC syndrome.

- ***Genetics*** – specialize in the diagnosis, management, and treatment of genetic conditions, such as CFC syndrome.
- ***Cardiology*** – specialize in the treatment and management of heart (cardiac) defects, including structural abnormalities with the heart, rhythm disturbances, and enlargement of the heart.

- ***Gastroenterology*** – specialize in the management and treatment of gastrointestinal (GI) abnormalities such as failure to thrive, feeding difficulties, and poor growth.
- ***Endocrinology*** – specialize in the evaluation and treatment of hormone abnormalities such as growth hormone deficiency and thyroid abnormalities.
- ***Dermatology*** – specialize in the evaluation, treatment, and management of skin problems such as dry skin, eczema, and moles.
- ***Neurology*** – specialize in the evaluation and management of problems related to the brain and nerves, including seizures, brain abnormalities, and muscle tone problems.
- ***Ophthalmology*** – specialize in the evaluation of problems related to the eye and/or vision, including strabismus (wandering eye), poor vision, and ptosis (droopy eyelids).
- ***Orthopedics*** – specialize in the evaluation and management of problems related to the muscles and bones, such as scoliosis (curvature of the spine), gait abnormalities, and joint problems.
- ***Otolaryngology*** – specialize in the evaluation and treatment of problems related to the Ear, Nose, and Throat (ENT), such as ear infections and breathing problems.
- ***Urology*** – specialize in the evaluation and treatment of kidney problems and undescended testes.
- ***Developmental/Behavioral*** – specialize in the evaluation and management of developmental disabilities and behavioral problems, such as delayed cognitive development, speech and language delays, attention deficit and hyperactivity disorder (ADHD), autism spectrum disorders, and sensory abnormalities.

Cardiac (Heart) Defects

A large majority of babies born with CFC syndrome have a heart defect. These can be characterized as congenital (present at birth) or may develop later. Although many different types of heart defects have been observed, the most common are pulmonic stenosis (PS), hypertrophic cardiomyopathy (HCM), and atrial septal defect (ASD).

The heart is a muscle that pumps deoxygenated blood to the lungs and oxygenated blood out to the body. Within the heart there are several valves that help to direct the flow of blood. A valve opens to let blood pass through and then closes to prevent the blood from flowing backwards. The pulmonary valve is located between the right ventricle and the pulmonary artery. Pulmonic valve stenosis is common in CFC syndrome. The valve is often small and underdeveloped (dysplastic), making it harder for blood to flow from the right ventricle to the lungs. Often, this is not severe and children do not require surgery. However, in a minority of

cases, surgery is needed to help restore proper blood flow. Surgeons can repair the valves, replace them with artificial valves, or increase their size by using a "balloon". In milder cases, balloon valvuloplasty is the preferred intervention for PS. A balloon tipped catheter is inserted into the valve. The balloon is inflated and the valve is widened, allowing more blood to pass through the valve.

The second most common heart defect associated with CFC syndrome is hypertrophic cardiomyopathy. In this condition the heart muscle is thickened and its function is impaired. Thickening of the heart walls leads to a decrease in the amount of blood able to be pumped out to the body. The degree of severity of HCM is variable. However, most people with CFC syndrome remain asymptomatic for many years.

Several other structural heart differences have been found in CFC syndrome. These are less common than pulmonic stenosis and hypertrophic cardiomyopathy.

Recommendations

It is recommended that anyone with a new diagnosis of CFC syndrome be referred to a cardiologist and receive an echocardiogram (ultrasound of the heart) and an electrocardiogram (ECG). If there are any abnormalities found, then routine follow-up is recommended (to be determined by cardiologist). If the initial studies are normal, then an echocardiogram should be repeated every 2-3 years throughout adolescence and every 3-5 years in adulthood.

Feeding and Nutrition

Severe feeding difficulties are common in the infant with CFC syndrome which may present as "failure to thrive". This may be related to poor sucking and/or swallowing coordination or difficulty with weight gain. Infants,

and occasionally older children, may require some assistance with the use of an NG (nasogastric) tube or G-tube (gastrostomy). Older children with CFC syndrome may also experience oral aversion to certain textures. This can often make feeding a difficult challenge for parents. Despite adequate nutrition and caloric intake, most individuals with CFC will be lower on the growth curves compared to siblings and other children their age.

Recommendations

If your child has any feeding difficulties, poor growth, or reflux, it is important to be evaluated by a gastroenterologist (GI doctor) and/or feeding therapist.

What about Growth and Other Hormone Functions?

People with CFC syndrome are generally shorter than average because they are genetically programmed to be small. The genetic mutations that cause CFC can affect growth hormone (GH) secretion or function. Some children have been found to have low GH levels. If your child has low GH levels, they might benefit from GH treatment. However, this should be discussed with an endocrinologist (a doctor who specializes in the function of hormones). At the present time, there is no data to document the success of GH therapy or to determine the incidence of growth hormone deficiency in children with CFC.

A delay in puberty may also be seen with CFC syndrome. Adolescents often go through puberty later than their peers. Once a person with CFC syndrome has matured into an adult, they may be able to have children. Data has not been obtained on a second generation of CFC syndrome individuals at this date.

Recommendations

If you have questions about growth or growth hormone therapy, your child's pediatrician can refer you to a pediatric endocrinologist to evaluate whether your child has any evidence of growth hormone deficiency. This is typically recommended at 2-3 years of age. If GH deficiency is found, a treatment trial is indicated. If not, opinions vary on whether treatment with GH would be effective. Growth hormone is, in any event, not a standard treatment of CFC syndrome. It is also recommended that children get thyroid hormone studies, since some individuals with CFC may have low thyroid hormone levels.

Skin Findings

A variety of skin manifestations are present in the syndrome. Not one feature is present in all cases, and there are a few individuals who have no skin abnormalities. A set of the most frequent manifestations observed in individuals who have CFC syndrome can be found below.

The hair is usually sparse, curly, and thin, has a lower posterior border, is dry, brittle, and grows slowly. Eyelashes and eyebrows are sparse, sometimes even absent. Nails are normal in most cases, but nail dystrophy has been reported in 15% of individuals with CFC.

Dry skin, keratosis pilaris (hair follicle prominence) and hyperkeratosis (thickened skin) are the most frequent skin features in CFC syndrome. Dryness of the skin is sometimes a predisposing fact for allergic dermatitis (eczema) so the use of powerful moisturizers is highly recommended. Keratosis pilaris varies in intensity from case to case. Some individuals have such a pronounced production of keratin in the hair follicle that the follicle itself becomes shut down, with no hair production. Keratosis pilaris can happen anywhere in the body (except over palms and soles, where there are no hair follicles), but is more frequently seen on the face (cheeks and eyebrows), arms and legs. Hyperkeratosis is also noted in different patterns. Most individuals have thickened skin on elbows and knees, others have thickened skin over the entire body, and very few have just palms and soles thickened.

Generalized hyperpigmentation is described in some individuals who have a darker skin color when compared to the rest of the family. But this is just a sign, leading to no complication or consequence. Hyperpigmented spots and cafè-au-lait spots (brown spots) are also reported, again with no complications related. Moles are also very common in CFC syndrome and may be present in non-sun exposed areas. They also appear to increase in number with age.

Blood vessel skin lesions such as hemangiomas and cutis marmorata (purple marks in a network pattern, over legs and arms) are also present in some individuals. There are no reports of hemangiomas needing treatment; they are more of the flat kind, leaving just a red to purple spot on the skin. Cutis marmorata gets worse when it is cold, so it is recommended to avoid exposure of the extremities, especially in winter. Again, no complications related to vascular skin manifestations are reported.

The lymphatic system is part of the circulatory system and is composed of vessels that carry lymph, a clear fluid, to the heart. Individuals with CFC syndrome can have abnormalities of this system, which may cause excess fluid to build up in different parts of the body. Some common areas for fluid build-up may include the back of the neck (particularly during pregnancy), which may be called a "cystic hygroma", or the lower limbs.

Recommendations

All individuals with a new diagnosis of CFC should have a consultation with a dermatologist to screen for hemangiomas and pigmented nevi (moles) with annual evaluations. If dystrophic nails are present or hyperkeratosis of the feet is severe, a referral to a podiatrist may be needed. If lymphedema is present, a referral to a vascular specialist is recommended. Special care should be given to the treatment of any skin infection.

Central Nervous System

At birth children with CFC syndrome often have a larger head size. CT scans or brain MRIs may show a lack of substance (particularly the cortex, which is known as the surface of the brain) and the cavities inside the brain are larger than usual. Thinning of the corpus collusum, the structure that separates the two halves of the brain, may also be seen in CFC syndrome. All of these findings are non-specific findings. The tests do not predict whether the child is going to have seizures or not. They do not predict the cognitive outcome and they do not predict the motor outcome.

Nearly 45% of children experience seizures. There are many different types of seizures that have been seen in CFC syndrome, including infantile spasms and tonic-clonic seizures. Most seizures begin in infancy or early childhood; however they may develop later in childhood as well. They are often controlled with medication; however some may be difficult to treat, even with several different medications.

Some individuals with CFC syndrome and other related conditions have sensory problems with the peripheral nervous system. The peripheral nervous system is a network of nerves that transmit information from the senses (i.e. hands and feet) back to the brain. If this system does not work properly due to damage of those nerves, symptoms may include temporary numbness, tingling, prickling sensations, and sensitivity to touch or muscle weakness.

Recommendations

Referral to a neurologist or epileptologist (seizure specialist) is recommended if there are seizures present. Families should be aware of the signs of seizures, particularly infantile spasms, which may consist of a sudden bending forward of the body with stiffening of the arms and legs; some children arch their backs as they extend their arms and legs. Spasms may occur upon awakening or after feeding, and often occur in clusters.

A brain MRI should be obtained if there is rapid head growth, infantile spasms, or changes in the child's neurologic examination. An electroencephalogram (EEG) is recommended if there is any suspicion of seizure activity.

If peripheral neuropathy is suspected, a referral to a neurologist is indicated to determine if nerve conduction velocities or an electromyogram is recommended to screen for the neuropathy.

The Eye/Vision

Nearly all individuals with CFC syndrome have some associated eye abnormalities. The most common findings are:

- Nystagmus (unsteadiness of the eyes)
- Hypertelorism (widely spaced eyes)
- Ptosis (droopy eyelids)
- Strabismus (muscle imbalance)
- Optic atrophy (under development of the optic nerve)
- Epicanthal folds (folded skin in corner of eye)
- Downslanting eyes
- Amblyopia (reduced vision)
- Small optic nerves (optic nerve hypoplasia)

Many of these contribute to the characteristic facial appearance seen in CFC syndrome. A majority of the individuals with CFC syndrome will need prescription glasses. Although ptosis and strabismus are not usually severe, in many cases surgery may be required.

Recommendations

Because of the high prevalence of eye problems, it is suggested that children with CFC syndrome be seen by a pediatric ophthalmologist. It is especially important to schedule a detailed eye exam in early childhood to assess the level of eye involvement in your child. Some of the CFC children have qualified for services from the teachers of the visually impaired. Check with your ophthalmologist to obtain his/her opinion on this service. Follow-up with the ophthalmologist is recommended every 6-12 months.

Skeletal/Orthopedic Findings

Children with CFC are at risk for scoliosis (curvature of the spine), flat feet (pes planus), joint contractures, and hip dysplasia. These can cause significant difficulty with walking that may require walking devices such as gait trainers or walkers. Some individuals with CFC have low bone

density, however, the exact incidence of this in individuals with CFC is unknown and requires additional research.

Recommendations

Referral to a pediatric orthopedist at the time of diagnosis to evaluate the presence of any orthopedic or skeletal abnormalities that may need to be followed over time. For individuals who are unable to walk, x-rays of the pelvis every two years are recommended to screen for hip dysplasia. A spine MRI should be performed prior to any spine surgery. Adolescents should have a bone density scan to screen for low bone density.

Hearing, the Palate and Speech

Mild hearing loss has been documented in individuals who have CFC syndrome. The hearing loss may be attributed to recurrent ear infections as well as heavy wax build up in the noted small (stenotic) ear canals. Recurrent ear infections and earwax build-up may result in speech delay.

The palate (roof of the mouth) may be high and narrow or even short or it may have a defect called sub-mucous cleft. This is where the tissues or bones in the midline of the palate have not closed, although the mucous membrane covering it is intact. These are sometimes difficult to detect and can contribute to speech and feeding difficulties. If your child is having difficulty with oral motor skills, feeding or swallowing you should find a speech language pathologist with particular expertise in these areas. Not all speech language pathologists have this background with oral motor therapy. To find qualified therapists in your area, you can contact the American Speech Language and Hearing Association.

Recommendations

Infants and children should have thorough hearing evaluations at the time of diagnosis and every 2-3 years or more frequently, if necessary. Medical management can sometimes minimize the speech delays that can result from the wax build-up and the recurrent ear infections. Referral to an otolaryngologist (i.e Ear, Nose, and Throat – ENT) is recommended for hearing loss management, to have the earwax removed, and medical management of the ear infections. Often the identification of a hearing problem can help explain some speech delay.

Renal/Genitourinary Findings

While kidney problems are not very common in CFC syndrome, some individuals have kidney malformations, kidney reflux, or undescended testes (cryptorchidism) in males.

Recommendations

A renal ultrasound to evaluate for kidney abnormalities is recommended at the time of diagnosis. Referral to a urologist is recommended if cryptorchidism is present.

Learning/Development

Doctors and teachers have timeline references for when a child should reach developmental milestones such as walking or talking. Frequently, children with CFC syndrome attain these milestones a bit later than usual. This is referred to as developmental delay. Sometimes children continue to be delayed and will be cognitively disabled. Other times, the children continue to progress and gain new skills.

Individuals with CFC syndrome may have near-normal or sub-normal cognitive abilities (IQ) and attend a regular school. Those with learning disabilities or cognitive disabilities may require extra help in some subjects. Sometimes children attend a resource room or have a classroom aide assigned to them in a regular classroom, while others might be in a self-contained setting. Educational teams often recommend therapies to help the children learn new skills. The therapy recommendations often depend on the amount of delay that the child is displaying.

Children with CFC syndrome have varying degrees of cognitive disability. Accessing the actual intelligence level can often be difficult since visual and language impairments can interfere with obtaining accurate results.

Delays in verbal expression are the most common learning disability in CFC syndrome. Many parents have reported that their child can understand verbal directions much better than they can express themselves. This suggests that receptive language skills (the comprehension of language) are noted to be better than expressive language and speech production skills (the ability to communicate clearly). It seems that many of these children are learning and storing language skills but are unable to indicate this knowledge until their expressive abilities improve. It is recommended that you stimulate your child's receptive and expressive language skills as much as possible. A speech language pathologist can give you specific suggestions to facilitate this development.

In addition, many children have delays in oral motor skills, meaning they have difficulty with range, coordination, and sequencing of the movements within the muscles and structures used for speech. These

difficulties can interfere with feeding and swallowing and with intelligible speech production.

Delays in fine motor skills (skills such as handwriting, feeding self, turning pages) and gross motor skills (such as crawling, walking, climbing stairs) may also be delayed. Mean age of walking without assistance is reported to be around 3 years, although ~18% of individuals with CFC are unable to achieve independent walking. Language abilities range from limited nonverbal communication to capacity to speak in full sentences. On average, children with CFC speak their first word around 2 years of age, although 10-30% may remain non-verbal. Progress in basic language development can continue into adolescence. Many families report using simple sign language or assistive technologies to facilitate communication.

Some of the delays in gross motor skills may be related to the degree of hypotonia (low muscle tone) in the child. Many children with CFC also have sensory processing problems which may include difficulties with certain textures, oral aversion, or sensitivity to sounds. Additional long term studies are needed in more children to determine if these numbers are an accurate reflection of the developmental delay in children with CFC syndrome.

Recommendations

Referral to early childhood services or local school system for needs assessment is recommended at the time of diagnosis. Children with learning disabilities and cognitive disability (often diagnosed in infancy as developmental delay), usually benefit from early intervention programs. These programs are designed to provide services to children at risk for developmental delays. Often, early intervention programs involve the help of professionals such as physical therapists, occupational therapists and speech language pathologists. By beginning these programs in infancy, children are able to reach their developmental milestones sooner and help them reach their ultimate potential.

Speech and language evaluation including assessment of oral-motor functioning, articulation, and expressive/receptive language ability as well as speech therapy are recommended. Sign language, communication boards and augmentative communication devices are often used with the younger children to reduce frustration. The children often can understand the language but without being able to express their own needs, they become upset. A speech pathologist with a background in communication devices can assist families with this transition phase.

Physical therapy with special attention to hypotonia and gross motor delay, and occupational therapy, with specific attention to sensory integration and vision concerns are very beneficial in helping children reach their milestones and their potential.

Upon school entry, a complete neuropsychological evaluation is recommended to determine the child's strengths, weaknesses, and areas that may need further attention. School professionals and families should develop an Individualized Education Plan (IEP) and revisit this plan as the child continues to progress throughout the school year.

Behavior

While many children with CFC do not have any behavioral concerns, some parents report behavior patterns such as irritability, attention difficulties, and obsessive or aggressive behaviors. Additionally, some children will have features of autism or autism-spectrum disorders. Sleep problems, such as poor sleeping, night sweating, and/or night terrors have been seen in many individuals.

Recommendations

If behavioral concerns exist, a formal behavioral assessment is recommended to develop a behavioral intervention plan and to determine what types of therapies might be most effective for that particular child. Treatments that focus on sensory concerns and communication skills may benefit children. In addition, if the child has the diagnosis of autism or features of autism, many services and resources that are available to children with autism-spectrum disorders may prove beneficial for children with CFC syndrome as well.

Management and Recommendation Summary

The following evaluations are recommended at the time of diagnosis and as needed during subsequent doctors' visits:

1. Genetics consultation and genetic testing
2. Complete physical exam including growth parameters
3. Cardiac evaluation including echocardiogram and electrocardiogram (EKG)
4. Neurologic evaluation with MRI of brain to detect any structural changes and EEG (electroencephalogram) if seizures suspected
5. Abdominal or renal ultrasound to evaluate for renal anomalies
6. Psychomotor development evaluation
7. Endocrine evaluation if growth delay is suspected
8. Ophthalmologic evaluation
9. Audiologic examination
10. Nutrition and feeding evaluation
11. Dermatologic evaluation
12. Orthopedic evaluation
13. Referral to Early Intervention Services

TABLE 1 Management Recommendations for CFC

Clinical Specialty	*Recommendations*
Genetics	**At risk for CFC based upon physical examination, developmental history, and medical history.**
At diagnosis:	• Genetics consultation. • Genetic testing directed by a geneticist/genetics provider using multigene Ras/MAPK pathway panel testing (if available). Approximately 80% mutation detection rate for CFC. • Consider sequential gene testing if panel testing is not available: (1) BRAF, (2) MEK1 andMEK2, and (3) KRAS • Parental testing if variant of uncertain significance is detected. • Consider high-resolution chromosome microarray if gene testing is negative. • If the above testing is negative, the geneticist/genetics provider can determine if exome sequencing is appropriate.
Ongoing management:	• Annual follow-up with geneticist/genetics provider or specialty Ras pathway clinic.
Cardiovascular	**At risk for pulmonary stenosis, HCM, septal defects.**
At diagnosis:	• Echocardiogram, electrocardiogram. • Consultation with a cardiologist if murmur present or if clinical features suggest CFC or other RASopathy.
Ongoing management:	• Cardiology follow-up if cardiac disease found at diagnosis or at each of the age intervals below. Cardiologist will decide on necessity for cardiac catheterization, interventional procedures, or surgical procedures depending on the individual cardiac abnormalities of each patient. • Infancy up to 1 y: If arrhythmias present, 24-h Holter evaluation. • Childhood and adolescence (up to 20 y): If no cardiac disease found initially, repeat echocardiogram every 2–3 y. Measurement of blood pressure at each visit. • Adulthood (20 y): Echocardiogram every 3–5 y if no previous heart disease found. Measurement of blood pressure at each visit.
Dermatologic	**At risk for keratosis pilaris, ulerythema ophryogenes, eczema, progressive multiple pigmented nevi, dystrophic nails, lymphedema, hemangiomas, hyperkeratosis, and generalized hyperpigmentation.**
At diagnosis:	• Consultation with a dermatologist. • Evaluation of hemangiomas. • Evaluation of pigmented nevi. • If lymphedema present, referral to vascular specialist/clinic.
Ongoing management:	• Frequent dermatology visits for management of xerosis, hyperkeratosis, and eczema. • Annual evaluation of pigmented nevi. • Referral to a podiatrist for dystrophic nails or hyperkeratosis if needed. • Monitor for lymphedema. • Meticulous skin care and early treatment of skin infection in the context of lymphedema. • Sun protection as recommended for the general population (ie, sunscreen; hats).

TABLE 1 Continued

Clinical Specialty	*Recommendations*
Neurologic	**At risk for infantile spasms, seizures, hydrocephalus, type I Chiari malformation, and other structural brain anomalies.**
At diagnosis:	• Referral to neurologist for a baseline evaluation. • Families should receive anticipatory guidance about the risk of seizures (infantile spasms, other seizure types) and other neurologic issues. • Brain MRI should be obtained in cases of rapid increase in head growth, infantile spasms, changes in neurologic examination, and regression of skills. • EEG if there is a suspicion of seizure activity. • Accurate seizure classification with clinical history and EEG to help guide medical management.
Ongoing management:	• Continued follow-up with neurologist for seizure management (if present). • In child with infantile spasms, consult with cardiologist for possible steroid management due to risk of cardiomyopathy. • If peripheral neuropathy suspected, consult with neurologist for nerve conduction velocities and electromyogram.
Cognitive and behavioral	**At risk for intellectual disability, delayed fine and gross motor skills, emotional and behavioral problems, atypical sensory processing, and speech/language impairments.**
At diagnosis:	• Referral to early childhood services or local school system for needs assessment and intervention. • Speech and language evaluation including assessment of oral-motor functioning, articulation, and expressive/receptive language ability. Speech and language therapy as indicated based on evaluation. For severe delays, consideration of alternative or augmentative communication systems. • Physical therapy (specific attention to hypotonia and gross motor delay). • Occupational therapy (specific attention to hypotonia, sensory integration, and vision concerns). • Behavioral therapy, mental health services, and/or alternative therapies may be considered to address behavioral, sensory, motor, social, emotional, and/or communication concerns.
Ongoing management:	• Continued evaluation and services by early childhood intervention programs in early childhood. • Upon school entry, physician referral for a full neuropsychological evaluation. • Upon school entry, school professionals and families should collaboratively develop an Individualized Education Plan (IEP) and/or other accommodation plan. Clarity should be established regarding medical diagnosis and eligibility for special education services. • If behavioral concerns exist, a functional behavior assessment may be indicated to assist in development of a behavior intervention plan (specific attention to sensory concerns, communication skills, and attentional ability).
Gastrointestinal	**At risk for feeding and/or swallowing difficulties, FTT, constipation, gastroesophageal reflux, and intestinal malrotation.**
At diagnosis:	• Nutrition assessment/growth measurements by primary physician. • Refer to gastroenterologist in early infancy for feeding difficulties, gastroesophageal reflux, and poor growth. • If feeding difficulties are present, referral for feeding therapy evaluation and recommendations. • Evaluate for gastroesophageal reflux and swallowing dysfunction by swallowing studies, pH studies, upper gastrointestinal series, and endoscopy studies as recommended by gastroenterologist. • Consider treatment with proton pump inhibitors for gastroesophageal reflux. • Consider assisted feeding for FTT (nasogastric or gastrostomy tube), found to be necessary in 40% to 50% with CFC. Surgical recommendations to be assisted by gastroenterologist. • If feeding difficulties are present, then refer for feeding therapy evaluation.

TABLE 1 Continued

Clinical Specialty	*Recommendations*
Ongoing management:	• Regular follow-up to monitor growth and nutrition. • Continued feeding therapy if there are persistent feeding difficulties. • Treatment of gastroesophageal reflux and constipation as needed as children get older.
Growth/ endocrine	**At risk for failure to thrive, short stature, GH deficiency, GH resistance, and delayed puberty.**
At diagnosis:	• Refer to endocrinologist between ages 2 and 3 y for growth monitoring or earlier if there are concerns about growth. • Obtain thyrotropin, free thyroxine, IGF-1, and IGF-BP3 levels because thyroid and GH abnormalities are seen in other RASopathies. • Nutritional assessment/growth measurements by primary physician.
Ongoing management:	• Monitor growth carefully (height, weight, and head circumference at each visit) and refer to appropriate specialists if significant change in growth curves (eg, endocrinologist, gastroenterologist, neurologist, or neurosurgeon). • Regular follow-up by endocrinologist if growth failure, GH deficiency, or thyroid hormone abnormality. • If growth failure: thyroid function studies, celiac disease screening, GH stimulation studies to be directed by endocrinologist. • Monitor pubertal development beginning around age 10 y.
Musculoskeletal	**At risk for hypotonia with decreased muscle, scoliosis, pes planus, joint contractures, hip dysplasia, and pectus deformities.**
At diagnosis:	• Referral to a pediatric orthopedist.
Ongoing management:	• Radiograph of thoracolumbar spine, pelvis and lateral radiograph of cervical spine depending on clinical findings of child. • For those who are not ambulatory: AP radiographs of pelvis every 2 y to monitor for hip dysplasia. • Monitor for scoliosis. • Spine MRI before any spinal surgery. • Long-term follow-up with orthopedist as appropriate. • Before orthopedic surgery, see hematologic recommendations. • Bone density scan in young adults.
Ophthalmology	**At risk for ptosis, amblyopia, refractive errors, strabismus, cataracts, optic nerve hypoplasia, optic atrophy, cortical visual impairment, delayed visual maturation, and abnormal depth perception.**
At diagnosis:	• Referral to a pediatric ophthalmologist. • Early intervention as appropriate (ie, correction of ptosis, prescription glasses for refractive errors or strabismus, patching for amblyopia).
Ongoing management:	• Follow-up every 6–12 mo or more frequently as recommended by ophthalmologist. • Visual functional assessment by early childhood programs and vision resources for poor vision and abnormal depth perception. • In those with optic nerve abnormalities, MRI of brain should be obtained to screen for malformations that could cause optic atrophy.

TABLE 1 Continued

Clinical Specialty	*Recommendations*
Otolaryngology/ audiology	**At risk for narrow ear canals, impacted cerumen, hearing loss, and laryngomalacia.**
At diagnosis:	• Audiologic evaluation. • Refer to otolaryngologist for airway evaluation/management in the case of neonatal or early respiratory issues. • Referral to otolaryngologist for hearing loss management.
Ongoing management:	• Audiologic assessment every 2–3 y, or more frequently if necessary. Hearing aids as needed. • Refer to otolaryngologist for impacted cerumen, abnormal audiologic testing, and hearing loss. • Prompt treatment of ear infections to minimize hearing loss. • Otolaryngology follow-up for management of airway.
Renal/ genitourinary	**At risk for kidney malformation, vesicoureteral reflux, and cryptorchidism.**
At diagnosis:	• Renal ultrasound to evaluate for structural renal anomalies. • Refer to urologist and endocrinologist if cryptorchidism present.
Ongoing management:	• As indicated by urologist.
Hematology/ oncology	**At risk for easy bruising, von Willebrand disease, and thrombocytopenia.**
At diagnosis:	• Obtain history regarding easy bruising or bleeding problems. • If easy bruising or bleeding problems are present, screen with CBC, platelet count, platelet function study, and von Willebrand screen. • Refer to a hematologist for an abnormal CBC.
Ongoing management:	• If evidence of easy bruising or bleeding appears with time, then screen with CBC, platelet count, platelet function study, and von Willebrand screen. • If patient requires surgery, screen with the above testing before surgery if not already done. • For those on divalproex sodium for seizures, obtain platelet count every 6 mo.
Dental	**At risk for malocclusion, posterior crossbite, and bruxism.**
At diagnosis:	• Dental evaluation.
Ongoing management:	• Appropriate hygiene. • Restorative care. • Orthodontic treatment as needed.

CBC – complete blood cell; FTT – failure to thrive.

Source: *PEDIATRICS® Official Journal of the American Acadmey of Pediatrics. http://pediatrics.aappublications.org/content/early/2014/08/26/peds.2013-3189*

Educating Yourself

How to share the news

When your child receives the diagnosis of CFC syndrome, it can be difficult to think about who to tell, when to tell, and how to share the news. The answer to these questions is based on your own personal preference and timeline. You might want to share limited information in the beginning and more information at a later date. Whatever you choose, there is no right or wrong way to do this and much of how it is done depends on your own comfort level. If you need suggestions or would like to discuss this with other parents, please let us know.

Web sites/online networking

The wonder of the Internet is that it can be an incredible source of information, as long as it is legitimate information. Resources on CFC syndrome and additional information will be provided at the end of this guide.

Become involved with CFC International

The amount and type of involvement is up to you. Some possible opportunities include serving as a board member, volunteering for different tasks or events (such as the CFC conference), or hosting a fundraiser. There are many different types of ongoing needs and the organization offers an incredible amount of support and information to help you get started. This is a great opportunity to make lifelong friends while helping to support a great cause that benefits your family. Please let us know what talents you possess - we can use your help and skills!

Fundraising

Since CFC is a rare disorder, research related to understanding, treating, and managing it is underfunded by pharmaceutical companies and the government. However, there is a great need for funding of basic laboratory research and clinical trials that may directly impact your child. Therefore, we encourage our families to fundraise to raise money to go towards CFC syndrome research or other CFC-related activities and events. Families may feel isolated when they get the diagnosis or they often feel that they are not able to do anything. Fundraising gives them an opportunity to not only help their child, but also help other children and families affected with CFC now and in the future. You may be surprised what a small dedicated group of individuals are capable of accomplishing!

Helpful Ways to Organize Information

CFC syndrome is a lifetime diagnosis and it can be very difficult to keep all of the testing, reports, and specialty physician visits organized. All medical records pertaining to your child are your property. Though some hospitals may charge an administrative fee for sending them to you, they cannot withhold them from you. Get copies or electronic versions of all physician reports, imaging studies (MRI, CT scan, echocardiogram, X-rays), operative reports, pathology reports, and genetic test results. A three-ring binder with tab dividers can be helpful to keep all of the specialists and results organized. Bring the binder to every physician visit and let them copy whatever reports are needed, and you have all the medical information at your fingertips that anyone would ever need. As health care becomes more digital, this will change with time. Have a note pad or recorder at every visit where you can write or record important information that is discussed during the visit, because you can only process so much in some visits. It is helpful to write any questions that you may have for the specialist you are seeing before the appointment so that you make sure you cover everything.

As a rule, physicians and medical centers have your child's best interests in mind; but always keep in mind that you, the parent, are the ultimate and most important advocate for your child.

Resources

CFC International

www.cfcsyndrome.org

Support group for individuals and families with CFC syndrome. Please check website for the most up-to-date resource information.

Global Genes

http://globalgenes.org

This non-profit organization promotes the needs of the rare disease community under a unifying symbol of hope – the Blue Denim Genes Ribbon™. What began as a grassroots movement in 2009, with just a few rare disease parent advocates and foundations, has since grown to over 500 global organizations.

RARE Toolkits

http://globalgenes.org/toolkits

Educational resources that provide critical information on various topics within the rare disease landscape. Some of which include:

- Parenting a Child with a Life-Limiting Illness
- Genetic Testing: Is This My Path to a Diagnosis?
- Searching for Answers: Contacting Biopharmaceutical Companies Effectively

National Organization for Rare Disorders (NORD)

http://www.rarediseases.org

The National Organization for Rare Disorders (NORD), a 501(c)(3) organization, is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

RASopathies Network

https://rasopathiesnet.org

RASopathies are a group of genetic syndromes that are as common as 1:1000. The RASopathy syndromes include: cardio-facio-cutaneous (CFC), Costello (CS), LEOPARD/NSML, Neurofibromatosis type 1 (NF1), and Noonan (NS).

CONCLUSION

Hopefully, this booklet has answered many of your questions about CFC syndrome. It is important for you to remember that you cannot control the genes you pass on to your children. Thus, there is nothing you can do prior or during a pregnancy that can cause or prevent the occurrence of CFC syndrome.

The diagnosis of a genetic syndrome is often difficult to accept. There is no right or wrong reaction. Feelings of sadness, anger, confusion, guilt, helplessness and fear may surface at once or in stages. Parents, siblings and/or extended family members may react toward the CFC child with rejection, embarrassment, over indulgence or in other ways.

Many parents find comfort and hope in talking to other families touched by CFC syndrome. The international support group is available to provide you with more resources, connections, and information regarding CFC syndrome.

This brochure is intended to provide basic information about Cardio-Facio-Cutaneous syndrome. It is not intended to, nor does it constitute medical or other advice. Readers are warned not to take any action with regard to medical treatment or otherwise based on the information in this brochure without first consulting a physician. CFC International, Inc. does not promote or recommend any treatment, therapy, institution or health care plan. The information contained in this brochure is intended to be for your general education and information only and not for use in pursuing treatment or course of action. Ultimately, the course of action in treating a given individual must be individualized after a thorough discussion with the individual's physician(s).

References

Online Mendelian Inheritance in Man (CFC entry): http://omim.org/entry/115150 . Online Mendelian Inheritance in Man (OMIM) is a database of human genes and genetic disorders written and maintained by medical professionals at Johns Hopkins and elsewhere, and developed for the Internet by the National Center for Biotechnology Information (NCBI). The information on this site is geared toward medical professionals.

Gene Reviews (CFC entry): http://www.ncbi.nlm.nih.gov/books/NBK1186/

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The information in this booklet is the most current available and is expected to change. To update yourself, please check with CFC International at: ***www.cfcsyndrome.org***.

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