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Cockayne Syndrome

Cockayne syndrome is a rare genetic disorder characterized by sun-sensitivity, abnormal growth, and premature aging. It occurs, on average, in only two per every million babies born in the United States and Europe. Those affected with Cockayne syndrome tend to have small heads (microcephaly), with small, deep-set eyes. They are of abnormally small stature, unable to gain weight and grow at a normal rate. They also have cognitive development problems and are thus mentally retarded.

The disease is split into three categories. Cockayne syndrome type I, also known as "moderate CS", involves an onset of developmental and growth abnormalities sometime in a child's first two years of life. The disease becomes progressively worse, and once it becomes fully developed, the affected child's height, weight, and head circumference are well below the fifth percentile. The patients are described as having "cachectic dwarfism," referring to their extremely skinny, small statures. Children with CS type I also have disproportionate limbs and a unique walking stance due to knee and other joint contractures. They have dry, thin hair and suffer from severe tooth decay. Hearing and vision loss also becomes progressively worse, as does the functioning of the central and peripheral nervous system, resulting in mental retardation. Patients with CS type I typically die within the first or second decade of their life.

Those affected with Cockayne syndrome type II, or "severe, early-onset CS," show symptoms from birth. They show signs of growth failure when they are born, and they have little neurological development after birth. Those affected with CS type II are often born with cataracts, and they typically develop kyphosis (hunchback) or scoliosis, as well as joint contractures. Their mental retardation is more severe, and in some cases they have no language skills and cannot sit or walk without assistance. They usually die by age seven.

The third type of Cockayne syndrome, or CS type III, is known as "mild" or "late-onset CS." It is a newly recognized form of Cockayne syndrome and is characterized by very mild growth and cognitive development abnormalities that appear later in childhood.

The classic diagnosis for most people with Cockayne syndrome rests on clinical findings within the first year or two after birth for CS type I patients, or at birth for CS type II patients. For patients with CS type III, diagnosis occurs later in childhood and can often be an uncertain diagnosis. There are two major criteria that must be present in the child or newborn in order for a diagnosis of Cockayne syndrome type I to be made. The first major criterion is abnormal postnatal growth, resulting in a height and weight that is under the fifth percentile by age two. The second major criterion is progressive microcephaly (abnormally small head circumference compared to body size) and neurologic dysfunction,

followed by progressive intellectual and behavioral decline. If those two major criteria are present in an infant or toddler, then a diagnosis of CS type I can be made, especially if the toddler also shows strong photosensitivity. In order to make a diagnosis of CS type I in an older child, in addition to the two major criteria the child must also have at least three of the CS minor criteria, such as cutaneous photosensitivity, hearing loss, dental decay, and an appearance of cachetic dwarfism.

A diagnosis of Cockayne syndrome type II is made when the infant is of small size at birth and shows little or no postnatal growth (height, weight, head circumference), as well as little or no postnatal neurologic development. Also, the presence of cataracts or other eye defects at birth serve to solidify a diagnosis of CS type II.

In addition to these clinical methods of diagnosis, some of the changes that occur in the brain as a result of Cockayne syndrome can be seen on brain scans. A family history of Cockayne syndrome also serves to bolster a diagnosis of CS.

The classic treatment for Cockayne syndrome consists of a mixture of symptom management and treatments or therapy to prevent the progression of symptoms. Patients often undergo physical therapy to maintain their ability to walk and to prevent joint contractures. They also have specialized education for their developmental delay. Patients must use sunscreens and sunglasses for their cutaneous photosensitivity and

to protect their lens and retina. They also often receive treatments for their cataracts and hearing loss. Those affected with Cockayne syndrome receive continuous dental care to minimize tooth decay. Sometimes, patients get gastrostomy tubes placed in them to help with feeding. Patients also take medications for spasticity and tremor if needed.

Cockayne syndrome is an autosomal recessive disease, meaning the mutation does not occur on one of the X or Y sex chromosomes and both parents must contribute a mutated copy of the gene in order for the child to exhibit a phenotype of Cockayne syndrome. Thus, the child of two carrier parents has a 25% chance of being affected with Cockayne syndrome. Since the disease is recessive, parents carrying one copy of the mutated gene typically do not show symptoms. There are two genes that can cause Cockayne syndrome if mutated: ERCC6 ("excision repair cross-complementing rodent repair deficiency, complementation group 6") and ERCC8 ("excision repair cross-complementing rodent repair deficiency, complementation group 8"). Mutations to ERCC6, located on the long arm of chromosome 10 at position 11.23, lead to Cockayne syndrome complementation group type B (CSB), which makes up about 65-75% of all Cockayne syndrome cases. Mutations to ERCC8, located on the long arm of chromosome 5 at position 12.1, lead to Cockayne syndrome complementation group type A (CSA), which makes up about

25-35% of all cases. Thus, Cockayne syndrome can result from mutations in either of these two genes.

The ERCC6 and ERCC8 genes code for proteins often referred to as the Cockayne syndrome B (CSB) and Cockayne syndrome A (CSA) proteins. These proteins are involved in transcription-coupled nucleotide excision repair. They interact with active genes, those genes undergoing transcription, and monitor for DNA damage. If they detect any damage during transcription, they repair it. If left unrepaired, the RNA polymerase, (the enzyme which carries out transcription), stops and the transcription process stalls. The CSA and CSB are thought to remove the stalled RNA polymerase and repair the damaged section of the DNA so that transcription can continue. There are many causes for DNA damage, from UV rays from the sun to radiation or toxic chemicals. Cells have DNA repair mechanisms in place to detect and repair the damaged DNA. In people with Cockayne syndrome, however, the mechanisms in place to repair the DNA damage, namely the CSA and CSB proteins, are not functional, either because the gene mutations cause them to be too short or because the mutations lead to the absence of certain amino acids. Thus, the damage in the DNA accumulates until the cells begin to malfunction and then die. The increased cell death is believed to be a key contributor to the symptoms of Cockayne syndrome.

Understanding the specific genetic causes of Cockayne syndrome has enabled advancements in the diagnosis of the disease. Gene tests can identify carrier parents in order to better inform couples before they decide to have a child. Prenatal diagnoses can also now be performed. In order to receive a prenatal test, however, a family history of ERCC6 or ERCC8 mutations must be identified. In one prenatal test, DNA is extracted from fetal cells obtained by amniocentesis during the 15th – 18th week of pregnancy, or chorionic villus sampling (CVS) during the 12th week of pregnancy. The fetal DNA can then be analyzed to see if it presents mutations in either the ERCC6 or ERCC8 gene. A prenatal diagnosis of Cockayne syndrome may also be made by testing the sensitivity of amniocytes to UV light. The ability of the amniocytes from fetuses affected with Cockayne syndrome are not as able to form colonies after exposure to UV light as the cells from normal fetuses. Studying the RNA synthesis in cultured amniotic cells after exposing them to UV light can also lead to a diagnosis of Cockayne syndrome. The cells of Cockayne syndrome fetuses do not display normal recovery in DNA and RNA synthesis after exposure to UV light. These prenatal tests deliver clear results that lead to a definite diagnosis of Cockayne syndrome.

Another test for Cockayne syndrome involves a DNA repair assay, in which fibroblast cells are tested for their sensitivity to UV light, their ability to synthesize RNA after damage from UV light, and their ability to

perform transcription-coupled repair. Molecular genetics testing is also performed, more for research purposes. Such tests involve sequence analysis of the ERCC6 and ERCC8 genes, followed by deletion/duplication analysis, in order to scan for mutations in these genes.

Though new understanding of the genetic causes for the disease have led to more comprehensive testing for Cockayne syndrome, better treatments have yet to be developed. For now, the treatments continue to consist of the traditional methods to manage most symptoms and prevent others from arising or worsening.

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