Cerebro-oculo-facio-skeletal syndrome

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Originally released January 21, 1998; last updated June 14, 2016; expires June 14, 2019

Introduction

This article includes discussion of cerebro-oculo-facio-skeletal syndrome, cataracts-microcephaly-kyphosis-limited joint movement, COFS, and Pena-Shokeir II syndrome. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

In this article, the author updates information on cerebro-oculo-facio-skeletal (COFS) syndrome. The condition is rare, with autosomal recessive inheritance, and manifests abnormal facies, ocular changes (eg, cataracts, retinal degeneration, microcornea, optic atrophy), in utero and postnatal growth retardation, severe psychomotor retardation, cerebral and cerebellar degeneration with calcification in basal ganglia and white matter, progressive joint contractures and wasting, and death in infancy or early childhood. In many instances, the disorder results from a mutation in the Cockayne syndrome group B (ERCC6/CSB) gene or xeroderma pigmentosum (ie, DNA repair) genes (ERCC2/XPD, ERCC5/XPG, ERCC1/XPF, or ERCC4), mirroring phenotypic and clinical similarities between these conditions.

Key points

• Cerebro-oculo-facio-skeletal syndrome is rare, with autosomal recessive inheritance, and manifests abnormal facies, ocular changes (eg, cataracts, retinal degeneration, microcornea, optic atrophy), in utero and postnatal growth retardation, severe psychomotor retardation, microcephaly with cerebral and cerebellar degeneration and calcification in basal ganglia and white matter, arthrogryposis with progressive joint contractures and wasting, and death in infancy or early childhood.

• The disorder results from a mutation in one of a number of genes, to date the Cockayne syndrome group B (ERCC6/CSB) gene or xeroderma pigmentosum (DNA repair) genes (ERCC2/XPD, ERCC5/XPG, ERCC1/XPF), reflecting phenotypic and clinical similarities between these conditions.

Historical note and terminology

Cerebro-oculo-facio-skeletal syndrome was first described by Pena and Shokeir in 1974. They identified 10 children, 9 of whom were from 2 families of North American aboriginal background residing in or near the province of Manitoba, Canada, with a uniform constellation of congenital abnormalities. On the basis of the apparent heredity and affected systems they entitled their paper “Autosomal recessive cerebro-oculo-facio-skeletal syndrome” (Pena and Shokeir 1974). This designation has been generally accepted. Since then, numerous case reports have dealt largely with clinical aspects of the disorder and its possible relationship to other disorders. A search for the molecular pathogenesis of the disorder advanced significantly in 1996, when XP was cloned (Gregg et al 2011). The ERCC (excision repair cross complementation) and XP (xeroderma pigmentosum) genes function as complexes that are essential to the repair of DNA (damaged by ultraviolet light, carcinogens, or mutagens) and, hence, are shown together in texts (Kirschner and Melton 2010; Fagbemi et al 2011).

Clinical manifestations

Presentation and course

Individuals with cerebro-oculo-facio-skeletal syndrome are usually identified at birth or shortly thereafter, on the basis of their physical appearance and severe psychomotor retardation. However, some may present prenatally (Laugel 2013). The appearance of those affected by the disorder is relatively characteristic and includes the major diagnostic criteria of (1) microcephaly; (2) ocular anomalies including cataracts, microphthalmia, optic atrophy, and blepharophimosis (Grizzard et al 1980; Insler 1987; Graham et al 2001); (3) dysmorphic facies with a high and broad nasal bridge, large ears, overhanging upper lip, and micrognathia; and (4) musculo-skeletal abnormalities including flexion contractures of the limbs (arthrogryposis), scoliosis, hip dysplasia or dislocation, narrow pelvis, short stature,
osteoporosis, dysplastic acetabula, and rocker-bottom feet with proximal displacement of the second metatarsals and longitudinal grooves in the soles along the second metatarsal. Infants may also have a short neck, hirsutism, widely spaced nipples, single palmar creases, axial hypotonia, peripheral hypertonia, and renal anomalies. Affected children are usually small at birth due to intrauterine growth retardation; growth progresses poorly in the postnatal period as well (Pena and Shokeir 1974; Preus 1990; Laugel et al 2008). Cyanotic edema, involving the extremities, appears to occur in patients with Cockayne syndrome, but not cerebro-oculo-facial-skeletal syndrome (Frouin et al 2013).

Affected infants may develop seizures including infantile spasms (Harden et al 1991). There is invariably severe motor delay. Few affected infants are capable of more than rolling over, and perhaps sitting, smiling, and learning a few words. Nevertheless, variable progression has led some authors to suggest that there are 2 subtypes of cerebro-oculo-facial-skeletal syndrome (Casteels et al 1991). Vision and hearing are often impaired. The children suffer from feeding difficulties and failure to thrive. In the terminal stages, the children may lose weight despite adequate caloric intake by tube feeding. Repeated respiratory infections eventually lead to death in infancy or early childhood, usually by 6 years, although one well-documented patient died at 11 years of age. At that time, it had become apparent that he resembled children with Cockayne syndrome in appearance and in regard to hypersensitivity to sunlight.

CT scan of the brain reveals enlarged ventricles and subarachnoid spaces with white matter hypointensity in the infantile period followed by progressive calcification in the basal ganglia, white matter, and sometimes the cortex (Linna et al 1982; Del Bigio et al 1997).

Laboratory findings are nonspecific and amino acid survey is normal. Patients may exhibit mild hepatic dysfunction, and liver biopsies may show fatty infiltration or mild cirrhosis (Pena and Shokeir 1974). Some cases have elevated creatine kinase levels in infancy and muscle biopsies show slight sarcomeric disorganization and fibrosis (Lerman-Sagie et al 1987; Gershoni-Baruch et al 1991). Bone biopsies show necrotic chondrocytes and loss of osteocytes (Hwang et al 1982).

The neuropathological findings in cerebro-oculo-facial-skeletal syndrome include: (1) severe microcephaly and mild ventriculomegaly evident from birth; (2) possible delayed myelination in cerebral structures with otherwise normal myelin structure; (3) swollen, PAS-positive ubiquitinated granular glial cells in the white matter which appear shortly after the onset of myelination; (4) subsequent patchy or diffuse loss of myelin with atrophy and gliosis in the white matter; (5) progressive cortical atrophy; (6) parenchymal, pericapillary, and vascular mineralization in the globus pallidus and putamen, cerebral cortex at the depths of sulci, and white matter; (7) rare binucleate Purkinje cells; (8) severe degenerative changes in the internal granular and Purkinje cell layers of the cerebellum; and (9) retinal degeneration with optic nerve atrophy (Del Bigio et al 1997). At birth and in infancy, the brains have a normal gyral pattern, cortical architecture, and cortical thickness suggesting that basic developmental processes are intact, although partial agenesis of the corpus callosum has been reported in 2 infants with cerebro-oculo-facial-skeletal syndrome (Surana et al 1978; Sakai et al 1997). Small brain size with ventriculomegaly at birth suggests that the degenerative process begins in utero. A mouse model resembles the human condition in both expression pattern of the XPG deletion and progression of neurodegeneration (Barnhoorn et al 2014).

Prognosis and complications

Prognosis can be difficult to ascertain, given the diversity of findings in the syndrome (Natale 2011). However, prognosis is uniformly poor for children who have been diagnosed positively with cerebro-oculo-facial-skeletal syndrome. The cause of this is not clear, but some phenotypic overlap is apparent in that cochlear changes can also be observed in Pena-Shokeir syndrome type I (Kaya et al 2016). Severe muscle weakness has been reported with end-stage muscle changes identified on biopsy (Longman et al 2004). Ichthyosis has been noted in 1 male patient (Suzumura et al 2006). Death ranges from the neonatal period to 6 years of age, although 1 child survived to 11 years of age. Most patients have severe cognitive and motor retardation and eventually die from respiratory illness. The cytotoxicity and DNA damage elicited by certain chemotherapeutic agents and radiation therapy trigger the nucleotide excision repair complex. Because ERCC1 is a major molecule in this pathway, mutations have a deleterious effect on the excision pathway (Faridounnia et al 2015). ERCC1 appears to play a prognostic or even carcinogenic role in some tumors (Metzger et al 2010; Rahn et al 2010). Because the helicase family of enzymes is important to pathogenesis, future patients may respond to chemical rescue to restore enzymatic activity (Suhasini and Brosh 2013a).
Biological basis

Etiology and pathogenesis

Cerebro-oculo-facio-skeletal syndrome, in most cases, is known or presumed to have a genetic basis. Most reported cases exhibit a familial tendency indicative of an autosomal recessive inheritance pattern (Lurie et al 1976). Parental consanguinity is common, but not universal. A striking Finnish lineage has been identified, with a single common ancestor (ie, founder effect) traced to the 18th century (Jaakkola et al 2010). Chromosomal studies have generally been normal, although a case with 47XXX was reported (Pena and Shokeir 1974; Pena et al 1978). A case of early onset Cockayne syndrome, with phenotypic similarities to cerebro-oculo-facio-skeletal syndrome, was also reported as 47XXX (Hayashi et al 1992). In both children, the chromosomal abnormality was considered to be coincidental. An Egyptian child with cerebro-oculo-facio-skeletal syndrome (and parents that were first cousins) was found to have a balanced translocation 46 XX t(1;16) (q23;q13), inherited from the mother. The authors suggested that the cerebro-oculo-facio-skeletal gene might be in the 1q23 or 16q13 region (Tentamy et al 1996). It has been shown that some affected children related to the Manitoba Aboriginal population group within which cerebro-oculo-facio-skeletal syndrome was originally reported have a mutation in the CSB gene, located on chromosome 10q11-21. The mutation results in truncation of the Cockayne syndrome group B protein. Nucleotide deletions in the same gene at other sites result in Cockayne syndrome (Cleaver et al 1999; Meira et al 2000). Other patients have been shown to have mutations in the xeroderma pigmentosum genes XPD and XPG, or in the ERCC1 (excision repair cross-complementing 1) gene (Suzumura and Arisaka 2010). Based on these findings, cerebro-oculo-facio-skeletal syndrome can be placed in a group of genetically and phenotypically related disorders, including Cockayne syndrome, xeroderma pigmentosum, and UV-sensitive syndrome (Wilson and Bohr 2013). However, it should be emphasized that these conditions form a phenotypic spectrum, without clear-cut diagnostic thresholds (Laugel 2013). The complexity of genotype-phenotype correlations depends upon several genetic factors, among which are genetic variations due to parental consanguinity and differences in allelic expression or methylation status (Schafer et al 2013).

Affected individuals exhibit degeneration of brain and bone beginning before birth, and generalized progressive wasting after birth. These features suggest that cerebro-oculo-facio-skeletal syndrome is a primary degenerative disorder affecting many cell types. The neuropathological changes and other phenotypic features are almost identical to those described in early-onset Cockayne syndrome (Preus and Fraser 1974; Dolman and Wright 1978; Patton et al 1989; Del Bigio et al 1997), and the 2 conditions are difficult to distinguish. Cerebro-oculo-facio-skeletal syndrome resides at the severe end of the spectrum, one whose heterogeneity is thought to be due to defects in DNA repair and transcription (Laugel 2013; Suhasini and Brosh 2013a). It has been known for some time that cell damage is important to pathogenesis. Cells from patients with cerebro-oculo-facio-skeletal and Cockayne syndrome exhibit defective growth in culture (Pena et al 1978) and are abnormally sensitive to ultraviolet radiation (Meira et al 2000). Cells with mutations in Cockayne syndrome group B are incapable of removing RNA polymerase II from sites of DNA damage (Cleaver et al 1999). Neurodegeneration occurs in other disorders of DNA repair including xeroderma pigmentosum (Itoh et al 1999). Because of these phenotypic similarities and the fact that patients with cerebro-oculo-facio-skeletal syndrome often have mutations in either the Cockayne syndrome group B gene (CSB) or the xeroderma pigmentosum genes (XPG, XPD, or XPF), it appears evident that these conditions (including trichothiodystrophy) be considered part of the spectrum of nucleotide-excision repair syndromes (Graham et al 2001; Suzumura and Arisaka 2010). All of these genes are involved in a variety of forms of DNA repair, including nucleotide excision repair, interstrand crosslink repair, and homologous recombination (Su et al 2012). Recent work has implicated DNA helicases, enzymes important to separation of the DNA and RNA helix, and therefore, a host of genetic processes, including transcription, translation, replication, recombination, as well as repair (Suhasini and Brosh 2013b). Thus, helicases play an important role in maintaining genomic stability (Suhasini and Brosh 2013b). The ERCC1 and ERCC4 genes encode for the enzyme ERCC1-XPF nuclease. Deletions are incompatible with life, whereas mutations lead to a variety of disorders (Manandhar et al 2015). Mutations in these genes are responsible not only for genetic disease but also some aging disorders and tumors. Because of the deleterious effect of ultraviolet light on cells, tumors are especially likely to develop in areas of the body exposed to light, for example, carcinomas and melanomas of the skin and eyes (Rapin 2013). It appears that nucleotide excision repair factors are also important to processes not associated with DNA damage; this may help explain the clinical diversity of syndromes (Hosseini et al 2015). Interestingly, isoforms of XPD, derived from corresponding mutations, can result in genetic rescue and milder phenotypes (Horibata et al 2015).
Epidemiology

Cerebro-oculo-facio-skeletal syndrome is very rare, with roughly 50 cases reported in the medical literature. The largest number of affected families has been among North American aboriginal populations of central Canada. Cases have also been reported in the United States (in both mixed-European and Afro-American backgrounds), Mexico, Finland, Italy, Egypt, Arabic countries, and Japan. Classification schemes continue to be developed (Natale 2011).

Prevention

Genetic counseling is the best means of prevention.

Differential diagnosis

Primary considerations are other syndromes with low birth weight, microcephaly, eye anomalies, and contractures. These include Neu-Laxova; Martsolf; Cataract, hypertrichosis, and intellectual disability; and MICRO syndromes. The latter condition is distinct from cerebro-oculo-facio-skeletal syndrome, differing in that neurologic degeneration is not as rapid and nucleotide excision repair studies in cultured fibroblasts are normal (Graham et al 2004). Progressive microcephaly and growth failure/developmental delay are diagnostic criteria for Cockayne syndrome, especially if other findings are present, including photosensitivity, enamel hypoplasia, progressive sensorineural hearing loss, pigmentary retinopathy and/or cataracts, and enophthalmia (Laugel 2013).

Diagnostic workup

Currently, the diagnosis of cerebro-oculo-facio-skeletal syndrome is made on the basis of accurate phenotypic description with the addition of a skeletal survey and neuroradiologic work-up. MRI is valuable in identifying and following cerebral and cerebellar atrophy and loss of white matter (Boltshauser et al 2002). Magnetic resonance spectrometry (MRS) has been used to demonstrate atrophy and hypo- or demyelination of white matter in affected patients (Rafique and Zia 2012). Cerebro-oculo-facio-skeletal syndrome has been suggested by ultrasound at 21 weeks (findings included microphthalmia, micrognathia, joint contractures, rocker bottom feet) and subsequently confirmed at autopsy (Paladini et al 2000). Skin may show café au lait macules (Twede and Difazio 2009). Skin biopsy for fibroblast culture is successful in assessing nucleotide excision repair and ultraviolet sensitivity, whereas pertinent mutations can be identified by molecular testing (Rapin et al 2000).

Management

Supportive care is indicated for feeding (gastrostomy), neurologic complications (poor vision and hearing, spasticity), and musculoskeletal (contractures) and respiratory complications.

Special considerations

Pregnancy

Because of the poor prognosis, it is unclear if affected females will reach reproductive age. Moreover, ovarian dysgenesis in one 10-month-old female does not offer an optimistic outlook (Boltshauser et al 2002).

Anesthesia

No specific information is available. Children with cerebro-oculo-facio-skeletal syndrome tolerate anesthetics for gastric, orthopedic, and ophthalmologic procedures.

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**References especially recommended by the author or editor for general reading.

** Former authors

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**ICD and OMIM codes

**ICD codes

ICD-9:
Other specified congenital anomalies: 759.8

ICD-10:
Other specified congenital malformation syndromes, not elsewhere classified: Q87.8

**OMIM numbers

Cerebro-oculo-facio-skeletal syndrome: #214150

**Profile

**Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years

**Sex preponderance**

male=female

**Family history**

family history typical
family history may be obtained

**Heredity**

heredity typical
heredity may be a factor
autosomal recessive

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

Neu-Laxova
Martsolf
Cataract
hypertrichosis
intellectual disability
MICRO systems

**Associated disorders**

Cockayne syndrome
Xeroderma pigmentosum

**Other topics to consider**

Ataxia
Aicardi-Goutieres syndrome
Cockayne syndrome
Idiopathic basal ganglia calcification
Pelizaeus-Merzbacher disease

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