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Cockayne syndrome: The expanding clinical and mutational spectrum

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ABSTRACT

Cockayne syndrome is a progressive multisystem disorder characterized by a specific cellular defect in transcription-coupled repair. Typical features include developmental delay, failure to thrive, microcephaly, cutaneous photosensitivity, dental anomalies, progressive hearing loss, pigmentary retinopathy, cataracts and enophthalmia. Various levels of severity have been described including the "classical" or moderate type I CS, the early-onset or severe type II and the mild or late-onset type III. Adult-onset cases with prolonged survival and normal initial development have also been identified. At the opposite end of the scale, the most severely affected patients, showing a prenatal onset of the symptoms, are overlapping with the cerebro-oculo-facio-skeletal (COFS) syndrome. These overlapping subtypes build a continuous spectrum without clear thresholds. Revised diagnostic criteria are proposed to improve the recognition of the disease. Two thirds of the patients are linked to mutations in the CSB (ERCC6) gene, one third to mutations in the CSA (ERCC8) gene. At least 78 different mutations are known in the CSB gene and 30 in the CSA gene to date, in more than 120 genetically confirmed patients. Large clinical and molecular databases are needed to unravel genotype-phenotype correlations and to gain more insight into the underlying molecular mechanisms.

1. Introduction

Cockayne syndrome (CS) is an autosomal recessive multisystem disorder characterized by mental retardation, microcephaly, severe growth failure, sensorial impairment, cutaneous photosensitivity, dental decay, recognizable facial appearance with deep sunken eyes. This progressive and devastating condition is related to defective DNA transcription and/or repair and belongs to the family of nucleotide excision repair disorders together with xeroderma pigmentosum (XP) and trichothiodystrophy (TTD). The first two patients were reported by Sir Edward A. Cockayne in 1936 and the disease was described as a cachectic dwarfism with retinal atrophy and deafness (Cockayne, 1936). In this original report and in clinically similar patients reported later on, the first symptoms typically occurred in early childhood. Most clinical features were already described in the first reports of the condition.

It is only from the late 1970s and early 1980s that the clinical diagnosis of CS could be confirmed by cellular testing, taking advantage of a particular sensitivity to UV light (Mayne and Lehmann, 1982; Schmickel et al., 1977). This defect in the transcription-coupled nucleotide excision repair then served as a definite hallmark to ascertain the diagnosis in all CS patients. Genetic confirmation only became available in the mid-1990s after the identification of the two major genes responsible for the disorder, ERCC6 (CSB) and ERCC8 (CSA) (Henning et al., 1995; Troelstra et al., 1992). These cellular and molecular findings provided the basis to expand the clinical spectrum of the disease beyond the framework of the initial descriptions. Early-onset cases (Lowry, 1982; Moyer et al., 1982) and late-onset cases (Kennedy et al., 1980; Rapin et al., 2006) were then identified and proved to share the same cellular defect than the classical patients. Early-onset cases and late-onset cases were named type II and type III respectively as compared to the classical (type I) patients described in the first place. Early-onset patients show congenital signs of the disease and late-onset cases may only be affected in late childhood or even adulthood. A comprehensive review of previously published cases led to the establishment of clinical diagnostic criteria in 1992 (Nance and Berry, 1992).

CS is a progressive disorder and most symptoms appear and worsen with time. Actually, all CS patients show very similar features but the time of onset and the rate of progression vary widely among the subgroups. With several hundreds of CS patients have been identified and clinically characterized, it has also become clearer and clearer that CS has a continuous spectrum of severity and that there is no clear threshold between the largely overlapping subgroups.

The limits of this constantly expanding clinical spectrum have been pushed even farther with the inclusion of very severely affected patients and very mildly affected patients who had been

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first considered as belonging to distinct entities. Cerebro-oculo-facio-skeletal syndrome (COFS) and UV-sensitive syndrome (UVSS) were described independently from CS in the 1970s and early 1980s (Fujiwara et al., 1981; Lowry et al., 1971; Pena and Shokeir, 1974), but eventually proved to share the same cellular defect as the canonical Cockayne patients (Graham et al., 1998; Itoh et al., 1994). COFS syndrome was first reported within the Manitoba aboriginal population as an autosomal recessive disorder defined by arthrogryposis, microcephaly, cataracts and microphthalmia. These features demonstrate a very early onset of the disease in the fetus. COFS patients show mutations mainly in CSB but also in XPD, XPG and ERCC1 (Laugel et al., 2008; Meira et al., 2000). UVSS is only characterized by cutaneous photosensitivity without any of the other features of the CS picture and without cancer proneness. It has been linked to mutations in CSB, CSA and a novel gene UVSSA (Horibata et al., 2004; Miyauchi-Hashimoto et al., 1998; Nakazawa et al., 2012; Nardo et al., 2009; Schwertman et al., 2012; Zhang et al., 2012). These entities are now considered as additional CS variants and appear to be the opposite ends of the same continuous spectrum, but they do not fully meet the canonical diagnostic criteria for CS anymore.

Finally, some rare patients show combined features of CS and XP, and are linked to mutations in XPD, XPB or XPG. Most XP–CS patients show a very severe phenotype, close to type II CS with severe skin photosensitivity (Lindenbaum et al., 2001; Vermeulen et al., 1993). XPB–CS and XPG–CS complexes have been associated with survival into adulthood with inconstant development of multiple malignancies (Rapin et al., 2006).

The minimal incidence of CS has been evaluated in Western Europe at 2.7 cases per million births (Kleijer et al., 2008). Higher incidences in recent years and in countries where diagnostic tests are routinely available suggest that CS is still likely to be underdiagnosed in many circumstances.

2. Disease characteristics

2.1. Facial appearance

The characteristic facial appearance of CS patients is mainly due to the loss of subcutaneous and orbital fat (Suppl. Fig. 1). The resulting enophthalmia is one of the most specific hallmarks for clinical diagnosis. However, it must be kept in mind that this facial appearance only develops with time (Suppl. Fig. 2) and may not be easily recognizable in the early stages of the diseases. It is also noticeable that COFS patients usually do not show the classical cachectic appearance. Appropriate tube feeding may also deeply modify this cachectic facial appearance but the enophthalmia usually persists.

2.2. Growth

Growth failure is a prominent and constant feature of CS and is considered as a major diagnostic criterion. It is also often one of the earliest signs of the disease. All patients show progressive growth retardation. Age of onset and growth rate vary among CS subgroups and parallels the severity of the other key symptoms. Usually, in types I and II, weight is affected slightly earlier and more severely than length/height. Conversely, short stature is predominant in mildly affected cases. It should be underlined that length or height measurements can be very inaccurate and often underestimated in CS patients due to joint contractures and that weight partly depends on nutritional management and neurological limitation of oral intake. Intra-uterine growth retardation is inconstantly observed in early-onset cases and is always followed by progressive growth failure in the early postnatal period. Body weight and length are typically normal at birth in type I and type III. Slowing of the growth rate is usually observed in the second year of life in type I patients and after 2 years of life in type III patients. Weight and height can reach an early plateau in the most severely affected patients. Moderate weight loss can be observed in the late stages of the disease. Even if the age of onset and growth rate vary among the subgroups, weight and height eventually reach a similar and very severe level in all groups, well below - 3 standard deviations, during infancy for type II patients, during childhood for type I patients and in their late teens for type III patients (Laugel, personal communication; Nance and Berry, 1992; Natale, 2011).

Body mass index is usually low in CS type I and II and in the normal inferior range in type III patients. The specific loss of subcutaneous fat is responsible for the "cachectic" appearance of CS patients and the BMI is often not as low as it appears to be, at least until the late stages of the disease.

Nutrition is a key issue for CS patients and their caregivers. Oral intake is often limited by swallowing difficulties particularly in the most severely neurologically impaired patients. Gastroesophageal reflux and recurrent vomiting are common in young CS patients and often require that they be given repeated small quantities of food. Gastrostomy tube feeding is routinely required in type II CS patients.

2.3. Nervous system

Developmental delay is another major diagnostic criterion for CS, leading to mild to profound intellectual disability. Secondary neurological deterioration and cognitive decline is common in later stages of the disease in all groups. The severity of the developmental delay is usually correlated with the overall severity of the disease. COFS and CS type II patients show very limited development. Poor feeding and weak cry are often present in the neonatal period, together with axial hypotonia and peripheral hypertonia. These patients are usually unable to sit or stand unaided and have no language or only very few words. CS type I patients show normal developmental milestones in the first months of life. Motor and speech delay can be observed at the end of the first year or during the second year of life. CS type I patients usually learn to walk but often lose this ability as the disease progresses. These patients can understand and make simple sentences. In spite of this developmental delay, CS patients are unanimously considered as outgoing and interactive in all reports, including the original paper by E. Cockayne (1936). CS type III patients may only have mild intellectual disability and learning difficulties in primary school. Some patients have even been reported to have normal intellectual capacities and should probably be considered as yet another subgroup of severity. Cognitive decline and early dementia in adulthood are often reported in the oldest patients of these categories, typically after 30 or 40 years of age.

CS patients also show many other symptoms of progressive neurological dysfunction. Most CS patients show a unique combination of pyramidal, extra-pyramidal, cerebellar and peripheral signs. Limb hypertonia and spasticity is an early symptom in the most severely affected patients. Briskness of tendon reflexes decreases rapidly as the peripheral nerve dysfunction progresses. Cerebellar signs such as gait ataxia, action tremor and dysarthric speech are almost constant in all CS patients, with various degrees of severity. Cerebellar ataxia can be an inaugural sign in the late-onset subgroup.

Seizures are usually not a major issue in CS patients even if seizures are probably slightly more common in CS patients than in the general population. No specific clinical or EEG pattern has been described.

Progressive microcephaly is a constant feature in CS patients. The absence of microcephaly at 3 years of age has been recognized