OPHTHALMIC MANAGEMENT OF COCKAYNE'S SYNDROME

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SUMMARY

Cockayne's syndrome is a rare, autosomal recessive condition which usually presents in early childhood, and is characterised by dwarfism, premature ageing, mental retardation and a typical facial appearance and body habitus. Retinal dystrophy, enophthalmos, strabismus, cataract, nystagmus and corneal opacities are associated ocular features. At a genetic level, a defect occurs in the pathway for the repair of transcriptionally active DNA, and the most common form of Cockayne's is associated with mutations in the human repair gene ERCC6. These patients pose a difficult management problem. A significant proportion will require cataract extraction at an early age, which may present technical difficulties due to enophthalmos, which is a constant finding, poor pupillary dilation and growth retardation. Also, the fitting and assessment of aphakic contact lenses during the post-operative period requires great skill. General anaesthesia in these patients may be hazardous. In particular, difficulty with endotracheal intubation should be anticipated. Two patients with Cockayne's syndrome requiring bilateral cataract extraction in early infancy are presented. The problems associated with surgery, anaesthesia and subsequent follow-up in these mentally retarded infants are discussed.

Cockayne's syndrome (CS)[1] is a rare autosomal recessive condition which presents in early childhood with growth failure, developmental delay and mental retardation.[2] Patients have a characteristic facial appearance often associated with microcephaly. Erythematous rashes due to photosensitivity are common and the skin may appear prematurely aged, being dry and scaly. The limbs are disproportionately long with flexion contractures, and kyphoscoliosis may develop. Neurological associations include sensorineural deafness, tremor, ataxia, spasticity, incontinence and normal-pressure hydrocephalus. Speech is progressively impaired and convulsions occur in 5–10% of cases.[3,4] The average age at death is 12 years.

Ocular features include enophthalmos, hyperopia, poor pupillary dilation and retinal dystrophy. Strabismus, cataracts and nystagmus have also been described. Other associations include optic atrophy or hypoplasia, corneal deposits and reduced lacrimation.[3,5–7] The presence of cataracts within the first 3 years of life, congenital structural eye anomalies, prenatal growth failure and severe neurological dysfunction from birth are recognised features of severe disease and early death.[3]

The ophthalmic management of such patients is complicated by their delayed neurological development, mental retardation and deafness. Anaesthesia is difficult due to problems with venous access and airway management. Two patients with early onset CS are presented and the management problems are discussed.

CASE REPORTS

Case 1

A 2-month-old female infant with CS, confirmed by skin biopsy, was referred to the eye department with bilateral cataracts. She was delivered at 36 weeks gestation by elective caesarian section, for premature rupture of membranes and breech presentation. At birth she was small for gestational age and weighed 2.3 kg. On the first-day examination, microcephaly, dysmorphic facial features and bilateral contractures of upper and lower limbs were noted. Feeding problems and failure to thrive were noted from birth, and associated with developmental delay and absent sucking reflex. Nasogastric feeding was instituted at 3 weeks of age following hospitalisation and treatment of an aspiration pneumonia.

Poor visual awareness was apparent soon after birth, and the baby showed no following response to

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a light source. There was no evidence of nystagmus or strabismus. Bilateral enophthalmos and small pupils which dilated poorly with cyclopentolate 0.5% and phenylephrine 2.5% were noted and bilateral cataracts of equal density were present. An electroretinogram showed a good response to flash and flicker, but VER showed no reproducible response. Assessment of visual acuity by preferential looking was not possible due to inattention.

Bilateral lensectomy, combined with lateral canthotomy, was performed and aphakic contact lenses were fitted on the second post-operative day. Visual responses, however, remained poor, although there was no evidence of retinal dystrophy. Contact lenses were assessed at weekly intervals, but contact lens fitting was technically difficult due to narrow palpebral apertures and small globe size. The eyes remained quiet and corneal sutures intact. Post-operatively, posterior capsule opacification resulted in dulling of the red reflex, and examination under anaesthetic was performed at 2 months following surgery, and combined with needling of the capsule and removal of sutures. The patient was kept under review, but following complications of aspiration pneumonia, died at age 10 months.

Case 2

An 11-month-old boy with CS confirmed by skin biopsy, a first cousin of our first case, was referred to the eye department and underwent bilateral lensectomy for congenital cataracts. He was born at 41 weeks gestation, following a normal delivery, and birth weight was low at 2.8 kg. The perinatal examination recorded microcephaly, dysmorphic facial features (Fig. 1) and bilateral lower limb contractures of hips, knees and ankles. Failure to thrive, developmental delay and feeding problems, mainly vomiting after feeds, soon became apparent. Recording of brainstem evoked response revealed moderate to severe sensorineural deafness.

Enophthalmos was present with manifest pendular nystagmus, and pupils were miotic, but reactive, and dilated poorly. There was no following response to a light source, and it was impossible to undertake a preferential looking assessment. The electroretinogram showed good response to flash and flicker, but VER revealed no clear reproducible response.

Following bilateral lensectomy, again combined with lateral canthotomy, contact lenses were fitted on the third post-operative day, after initial difficulty, and the patient was reviewed weekly. However, due to problems with insertion and removal of the lenses, contact lens wear was abandoned at 2 weeks post-operatively and the patient was prescribed aphakic spectacles. Post-operatively, a following response to light was demonstrated, and funduscopy showed no evidence of retinal dystrophy. At 5 months he underwent further surgery to remove a posterior capsule plaque in addition to suture removal.

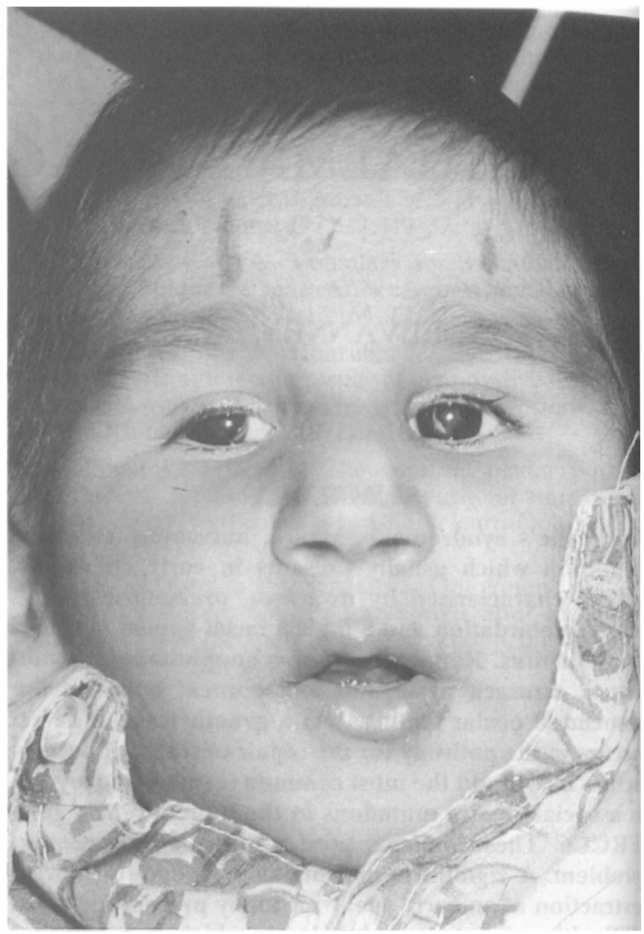

Fig. 1. *Case 2. Facial features.*

DISCUSSION

CS is heterogeneous and three complementation groups (A, B and C) have been identified. Group B is the commonest type and accounts for most of the cases of CS.[8] Additionally, CS is increasingly being divided, on clinical grounds, into type I (CSI) and type II (CSII).[3] CSI, which is the typical presentation, is also known as classical CS, with onset during the second year of life, often preceded by a normal first year.[6,7] CSII occurs either prenatally or in early infancy and is associated with low birthweight, ocular pathology, increased severity and poorer prognosis.[9,10] The two cases reported here are both CSII.

Ophthalmic management may be difficult. The presence of cataracts early in life is a poor prognostic sign in CS and indicates a shortened life expectancy. In a recent review of 140 cases of CS, of 22 patients who developed cataracts before 3 years of age only 2 were known to live beyond the age of 7 years.[3]

Cataract surgery in these infants is technically more demanding, as enophthalmos may hinder adequate exposure of the eye, and lateral canthotomy and a temporal approach may be necessary to

improve surgical access. Poor pupillary dilation is another significant factor, and may cause difficulty with removal of the anterior lens capsule.

The insertion of intraocular lenses in children remains controversial, and their use is generally reserved for children over 2 years of age.[11,12] Rapid opacification of the posterior lens capsule necessitates an adequate central posterior capsulotomy, and in the two presented cases this was performed at the time of initial lens aspiration. Both cases required further capsule surgery post-operatively.

The fitting of aphakic contact lenses in these small babies requires great skill. In addition, enophthalmos and narrow palpebral apertures may complicate the situation. Our first case was successfully fitted with contact lenses in the initial post-operative period, but technical difficulties associated with fitting necessitated a change to aphakic spectacles in both cases.

Early detection of contact lens induced infection or suture-related problems is essential in the post-operative evaluation of babies undergoing cataract surgery, and frequent assessment is necessary. Repeated examinations under anaesthetic may be required for adequate ocular examination, and liaison with the paediatric anaesthetic service is important. Early suture removal is recommended to reduce the risk of potentially sight-threatening infection.

Pigmentary retinal degeneration in CS, giving a 'salt and pepper' appearance to the retina, is progressive, and a normal fundal appearance in early life does not exclude the diagnosis.[3] Visual prognosis in these patients is, therefore, poor. Cataract surgery performed at an early stage, before the progression of the retinal dystrophy, ideally within the first 3 months of life to reduce the risk of deprivational amblyopia, offers the best visual outcome. However, accurate visual assessment in these babies is extremely difficult due to mental retardation and sensorineural deafness.

Anaesthesia for patients with CS requires careful consideration. Peripheral venous access may not be easy due to the patient's small size, previous multiple venepunctures, and the presence of limb contractures. Airway problems and difficult endotracheal intubation are to be expected.[13] There is also an increased aspiration risk, due to feeding problems associated with regurgitation and vomiting. Aspiration of feed together with kyphoscoliosis predisposes to frequent chest infection. Additionally CSII patients are at increased risk of intraoperative hypothermia, due to their small size. Renal disease and hypertension are also documented associations of CS which need to be assessed.[14]

In both our patients peripheral venous access was difficult, and use of an oropharyngeal airway was necessary during gaseous induction. Endotracheal intubation was difficult in each case, being grade III according to the Cormack and Lehane classification.[15]

Recent progress in the genetics of CS has shown the defect to lie in the pathway for repair of transcriptionally active DNA. A mutation in the human repair gene ERCC6 is thought to be the primary cause of most cases.[16] ERCC6 is located on the long arm of chromosome 10 (10q11-q21).[17] It specifically functions in the process of nucleotide excision repair. This process repairs the transcribed strand of active genes by excising and replacing damaged nucleotides in the DNA sequence. Neurodegeneration appears to be associated with the loss of preferential repair of active genes.[18]

It has been postulated that damage to photoreceptors and to the iris is caused by UV light induced DNA and RNA replication defects, so that in the absence of adequate recovery of DNA and RNA replication, cells receiving large amounts of UV light will degenerate, giving rise to the observed ocular findings.[5]

A diagnostic test is now available for CS. It is usually performed on cultured fibroblasts obtained from a 4 mm skin punch biopsy specimen, and is based on the differential response of RNA synthesis in normal and CS cells following a standard exposure to UV radiation.[19,20] By applying the same test to amniotic fluid cells, prenatal diagnosis is also possible. Unfortunately, at present, there is no test to identify the heterozygous carriers of the CS gene. Currently, treatment for CS is purely supportive, and recent advances in the understanding of its genetics will help in the counselling of parents. Future management may lie in the area of gene therapy,[21] which may provide definitive treatment for this disabling and lethal condition.

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