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Congenital cataract and multisystem disorders

LORRAINE CASSIDY, DAVID TAYLOR

Abstract

A knowledge of those syndromes associated with congenital cataract is essential for the paediatric ophthalmologist, as congenital cataracts are manifest in a large number of syndromes. It is important to have the correct diagnosis in such cases, not only for genetic and prognostic information, but also in order to help the parents to understand their child's condition. This paper describes the more common syndromes seen in association with congenital cataract, and emphasises the importance of looking at the whole child and family. We aim to provide a practical clinical guide to the diagnosis of hereditary and non-hereditary syndromes associated with congenital cataract.

Key words Congenital cataract, Dermatological disease, Dysmorphic, Hydrocephalus, Microcephaly, Polydactyly, Short stature

Congenital cataract may be important in itself, but may also have wider significance and be part of a multisystem disorder. Parents should be questioned in detail about the pregnancy, family history and whether they feel that their child is developing normally, and if the child has any other health problems. Parents, patient and any accompanying siblings should be observed, and any dysmorphic features, no matter how subtle, noted. There are many syndromes associated with congenital cataract that may have implications for the child's health and survival, and for risk to other potential offspring.

The use of a dysmorphology database[1] may facilitate the definition of an already known syndrome, which may help with prognosis and genetic counselling. In 1998 there were 274 syndromes associated with cataract.[1] The various dysmorphic conditions more commonly associated with congenital cataract are listed in Table 1. This discussion will concentrate only on the associated dysmorphic syndromes. Metabolic and some neurological disorders associated with congenital cataract but without dysmorphic features will not be considered.

L. Cassidy
D. Taylor
Department of Ophthalmology
Great Ormond Street Hospital for Children
London, UK

Mr David Taylor ✉
Department of Ophthalmology
Great Ormond Street Hospital for Children
Great Ormond Street
London WC1N 3JH, UK
Tel: +44 (0)171 405 9200, ext 8651
Fax: +44 (0)171 829 8647
e-mail: dtaylor@vissci.ion.ucl.ac.uk

Table 1. *Dysmorphic syndromes associated with congenital cataract*

I. Congenital cataract and dysmorphic facial features
1. Trisomy 21
2. Hallermann–Streiff–François syndrome
3. Lowe's oculo-cerebro-renal syndrome
4. Nance–Horan syndrome
5. Smith–Lemli–Opitz syndrome
6. Congenital cataract, microphthalmia, septal heart defect and dysmorphic facial features
7. Martsolf's syndrome

II. Congenital cataract and short stature
1. Chondrodysplasia punctata (rhizomelic and non-rhizomelic forms)
2. Autosomal recessive mental retardation, cataract, ataxia, deafness, polyneuropathy and short stature
3. Cataract, sensorineural deafness, hypergonadism, hypertrichosis and short stature
4. Marinesco–Sjögren syndrome
5. Majewski syndrome
6. Conradi's/Conradi–Hunermann syndrome
7. Pollitt syndrome
8. Martsolf's syndrome

III. Congenital cataract and microcephaly
1. Autosomal cerebro-oculofacial skeletal syndrome (CFS)
2. Autosomal recessive congenital infection-like syndrome
3. Autosomal dominant microcephaly, eye anomalies (congenital cataract and coloboma), short stature and mental retardation
4. Autosomal recessive congenital cataract, mental retardation, motor, sensory and autonomic neuropathy
5. Early-onset Cockayne syndrome
6. Cri-du-chat syndrome (5p deletion)
7. Autosomal recessive cataract, microcephaly, renal tubular necrosis and encephalopathy with epilepsy
8. Czeizel–Lowry syndrome
9. Edwards syndrome
10. Autosomal recessive sutural cataracts, retinitis pigmentosa and microcephaly
11. Autosomal recessive microcephaly and congenital cataracts, kyphoscoliosis and failure to thrive
12. Autosomal recessive microcephaly, microcornea, congenital cataract, mental retardation, optic atrophy and hypogenitalism
13. Microcephaly, microphthalmia, cataracts and hypogenitalism
14. Autosomal recessive ataxia-microcephaly-cataract syndrome
15. Martsolf's syndrome

IV. Congenital cataract and digital abnormalities
1. Majewski syndrome
2. Smith–Lemli–Opitz syndrome
3. Schachat and Maumenee's patient: congenital cataract, mental retardation, obesity, hypogenitalism, skull deformities and polydactyly

V. Congenital cataract and dermatological disease
1. Conradi's/Conradi–Hunermann syndrome
2. Chondrodysplasia punctata
3. Pollitt syndrome
4. Menke's disease
5. Hypertrichosis and congenital cataract
6. Alopecia, hyperkeratosis and congenital cataract

VII. Congenital cataract with hydrocephalus or skull deformities
1. HEC syndrome
2. Craniosynostosis and congenital cataract
3. Martsolf's syndrome
4. Hydrocephalus, congenital cataract and microphthalmia

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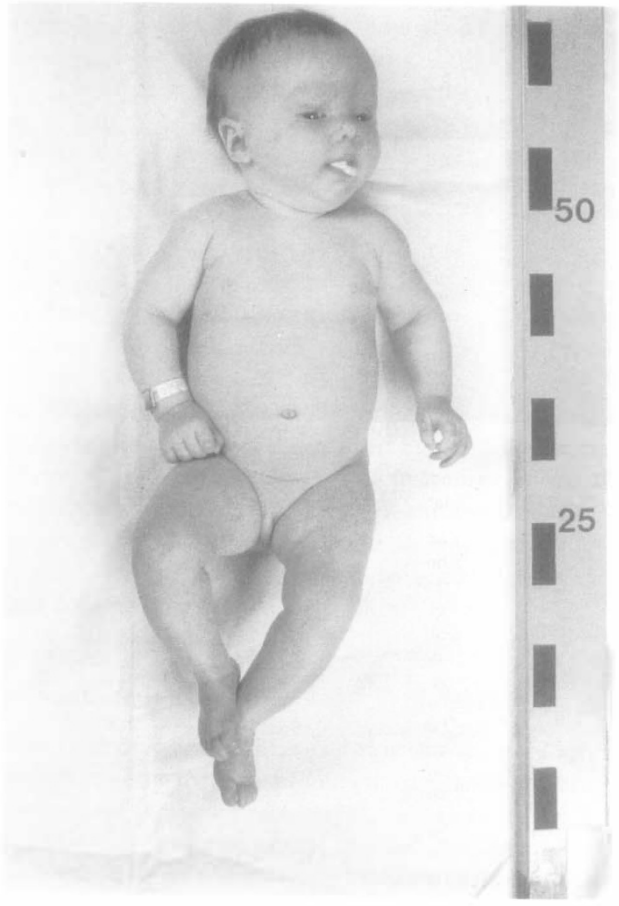

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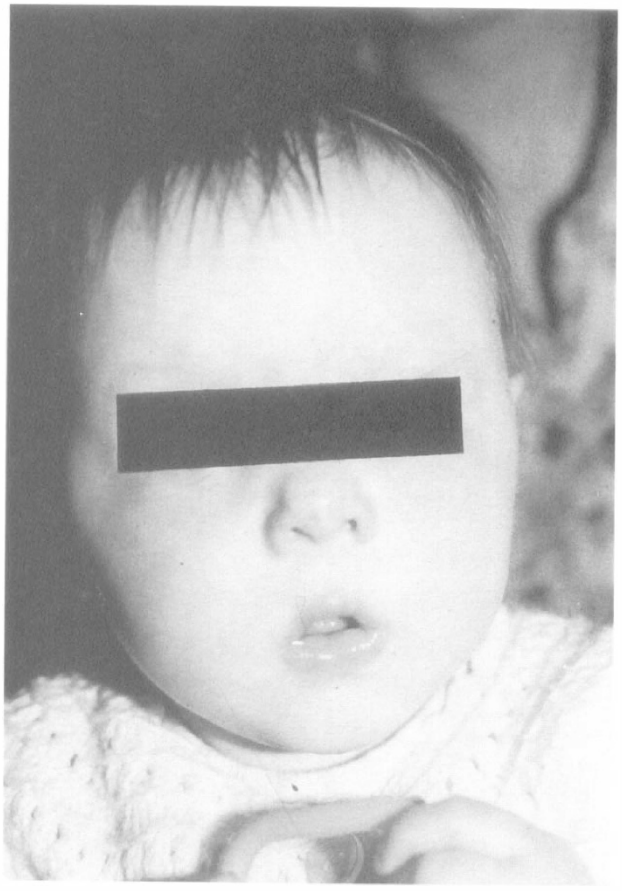

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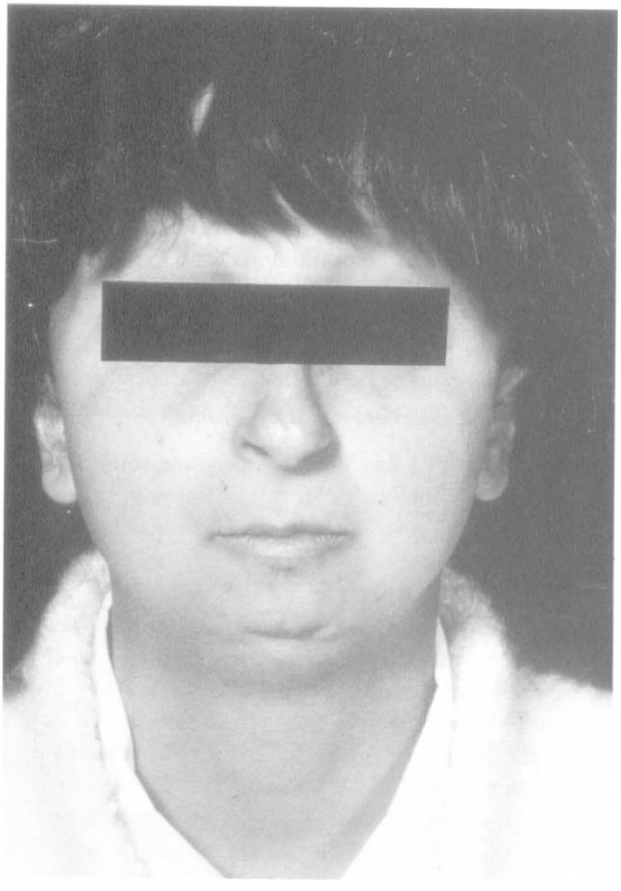
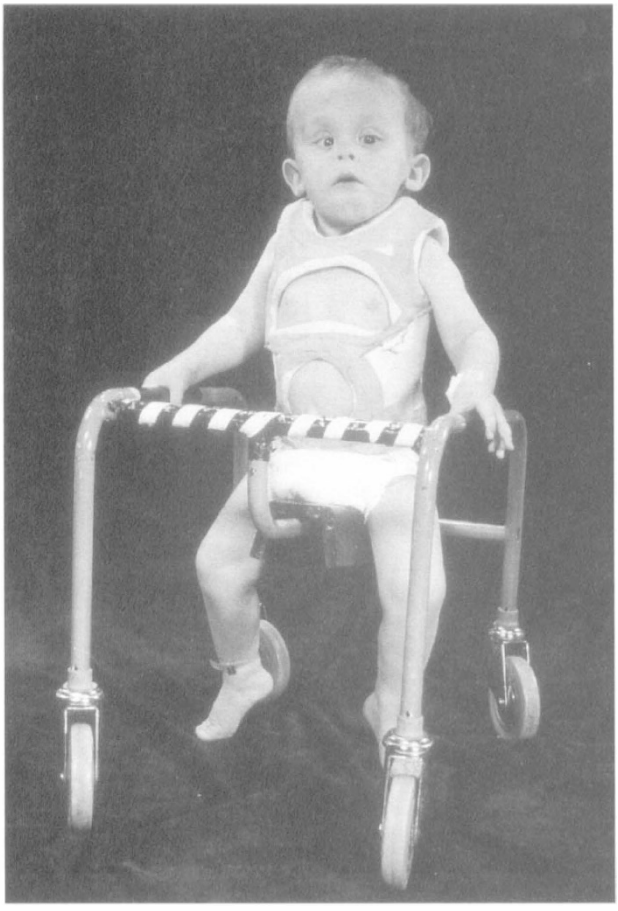


(c)

Fig. 1. *(a) Infant with Hallermann–Streiff syndrome. This baby presented with congenital cataracts; no syndrome was suspected initially as the child appears to be normal. (b) The same child 1 year later, when the characteristic facial features are becoming noticeable. (c) In adulthood the facial features of Hallermann–Streiff syndrome are easily recognised.*



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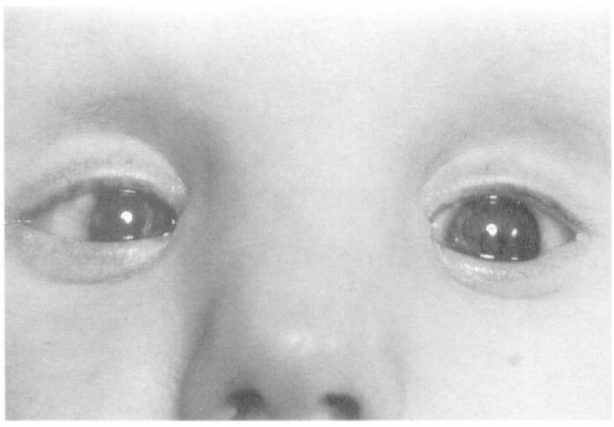


(b)

Fig. 2. *(a) A child with Lowe's syndrome who did not develop aminoaciduria until late infancy. (b) The same child after right cataract surgery. Notice the sunken eyes, left cataract and small pupil.*

Dysmorphic syndromes associated with congenital cataract

There are many dysmorphic syndromes that include congenital cataract; those with common features will be grouped together for simplicity.

I. Congenital cataract and dysmorphic facial features

1. Down syndrome/trisomy 21

There is an increased incidence of congenital cataract in children with Down syndrome.[2–7] The reported frequency ranges from 2% to 6%.[4,6] Merin and Crawford[7] found that of a series of 386 cases of congenital cataract, 4% of the total number of patients had Down syndrome. The characteristic features of this disorder include upward-slanting palpebral fissures, epicanthic folds, flat midface with relative prognathism, brachycephalic skull with flattening of the occiput and a protruding tongue. The hands are typically short and broad, with an abbreviated and clinodactylous fifth finger. These children also have hypotonia, cardiac anomalies, dermatoglyphic alterations and an absent moro reflex.

2. Hallermann–Streiff–François syndrome

This syndrome (Fig. 1) is characterised by frontal prominence, small beaked nose, prominent veins, baldness, progeria, micrognathia and pointed chin, short stature, hypodontia and blue sclera. It is the frontal prominence, the thin pointed nose and the small chin that are most suggestive in a baby, especially in the presence of microphthalmia and cataracts. Congenital cataracts are usually bilateral and occur in between 81% and 90% of cases.[8–13] Mental retardation may occur in about 15% of cases. Cohen[8] reviewed 150 cases and suggests that the incidence of the various manifestations is cataract 81–90%, microphthalmia 78–83%, dental anomalies 80–85%, hypotrichosis 80–82%, skin atrophy 68–70% and short stature 45–68%.

3. Lowe's oculo-cerebro-renal syndrome

Typical features of this X-linked recessive condition in males include chubby cheeks, frontal bossing, hypotonia, mental retardation, aminoaciduria and renal tubular acidosis with hypophosphataemia, congenital cataract, mesenchymal dysgenesis and glaucoma.[14] The aminoaciduria may be an inconstant feature in infancy (Fig. 2a). The majority of affected individuals are moderately to severely mentally retarded.[15] Even during infancy the eyes are characteristically sunken (Fig. 2b). Congenital cataract, which is typically a flattened discoid or ring-shaped opacity, often associated with glaucoma and a miotic pupil, is a well-established feature of Lowe's syndrome.[16] Heterozygous females may have finer lenticular opacities and posterior lenticonus-signs that can be used for carrier detection.[16–21] More than a hundred opacities, tending to be located in the equatorial

area of the lens, are considered to be good evidence of carrier status,[17] but their absence does not exclude carrier status. Occasionally females have been reported with early features of the condition, but go on to develop a mitochondrial cytopathy;[22] this is most likely to be a phenocopy.

Tripathi *et al.*[16] suggest that the existence of congenital cataract in affected patients, long before systemic metabolic and biochemical abnormalities become evident, and the presence of characteristic lens opacities in female carriers who have no apparent biochemical or systemic disorders, points towards a primary lens defect in the lens cells. This group believe that the pathogenesis of Lowe's cataract can be explained by the deactivation of one of the X chromosomes early in embryogenesis. In males, because there is no normal X chromosome to nullify the effect of the Lowe gene, all lens cells become affected, whereas in the carrier female only some of the lens cells become affected.

4. Nance–Horan syndrome

This form of X-linked cataract[23–25] is characterised by supernumerary incisors, prominent ears, anteverted pinnae and shortened metacarpals in males. Carrier females have posterior sutural lens opacities, shaped like an inverted 'Y' in some (Fig. 3). Posterior lenticonus may be a feature.[26] Obligate carriers have widely spaced teeth that are either cone-shaped or shaped like the blade of a screwdriver. A small proportion of affected males are mentally retarded. The gene has been mapped to Xp22.[27,28]

5. Smith–Lemli–Opitz syndrome

This rare syndrome is an autosomal recessive condition resulting from a disorder of cholesterol metabolism at the level of 3-β-hydroxysteroid-Δ-reductase, resulting in elevated levels of 7-dehydrocholesterol.[29,30] It is characterised by cleft palate, cataracts,[31–35] hypospadias, post-axial polydactyly, and a distinctive craniofacial appearance of microcephaly with bi-temporal narrowing, ptosis, strabismus, epicanthus, anteverted nostrils, a broad nasal tip, prominent lateral palatine ridges and micrognathia.

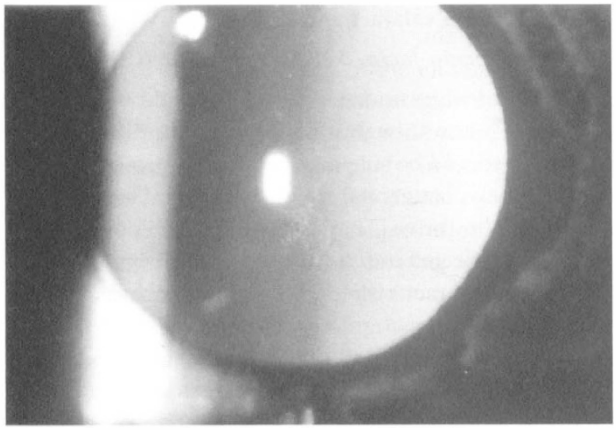


Fig. 3. *Sutural lens opacities in the mother of a child with Nance–Horan syndrome.*

In the hands the index finger can overlap the middle finger and the thumb can be short with a short first metacarpal. There is significant 2–3 syndactyly of the toes. Various internal malformations have been reported including pyloric stenosis, pancreatic anomalies and lung segmentation defects.

There is evidence for two separate types. That described above is referred to as type I; type II is lethal in the neonatal period.[36,37] Prenatal diagnosis has been reported by measuring 7-dehydrocholesterol levels in amniotic fluid.[30,38–40]

6. Congenital cataract, microphthalmia, septal heart defect and dysmorphic facial features

Wilkie *et al.*[41] described a mother and daughter with atrial septal defects, microphthalmia, bilateral congenital cataracts and dysmorphic facial features, which included mild macrocephaly, bilateral ptosis, a narrow prominent nose with broad colmella and notched alae nasae, antimongoloid slanting of the palpebral fissures and high-arched narrow palate.

II. Congenital cataract and short stature

1. Chondrodysplasia punctata (rhizomelic form and non-rhizomelic form)

A. Rhizomelic form

This autosomal recessive lethal form of chondrodysplasia punctata is characterised by symmetrical rhizomelic shortening of the limbs with enlarged joints and contractures. Facial features include a mongoloid eyeslant, a depressed nasal bridge, hypertelorism, anteverted nostrils and full cheeks. There may be ichthyosiform skin changes. Congenital cataracts occur in 72%.[42,43] At birth radiographs reveal flared metaphyses with epiphyseal stippling, and there may also be stippling adjacent to the ischial and pubic bones and in the region of the larynx and sternum. Coronal clefts of the vertebrae are marked. In later infancy the bones become demineralised, the vertebrae become flattened and the epiphyseal stippling disappears. About two-thirds of patients die in the first year of life with others dying in late infancy; survival beyond 5 years is rare. Survivors develop microcephaly and mental retardation. Pathological studies reveal abnormal peroxisomes in the liver. Reduced phytanic acid oxidation, defective plasmalogen synthesis and the presence of the unprocessed form of peroxisomal thiolase can be demonstrated. Acyl-CoA:dihydroxyacetone phosphate acyltransferase (DHAP-AT) levels are reduced.

(a) (b)

Fig. 4. *Typical facial features (a) and rocker-bottom feet (b) of a child with COFS/early-onset Cockayne syndrome.*

B. Non-rhizomelic form

These infants have the biochemical features of rhizomelic chondrodysplasia punctata but with a milder phenotype and no obvious limb shortening.[44–47] The form is characterised by predominantly epiphyseal, asymmetric calcifications and dysplastic skeletal changes associated with cataracts and skin changes.[42,43] In two series described[44,46] the affected individuals have expressionless faces and all the infants had cataracts. Joint stiffness was progressive and there was some spasticity of the limbs. The prognosis for life is good and affected individuals have normal intelligence.

2. Autosomal recessive mental retardation, congenital cataract, ataxia, deafness, polyneuropathy and short stature[48]

3. Cataract, sensorineural deafness, hypogonadism, hypertrichosis and short stature[49]

4. Marinesco–Sjögren syndrome

The features of this autosomal recessive condition are cerebellar ataxia, congenital or infantile cataracts, short stature and mental retardation.[50–52] There may also be muscle wasting and distal muscle weakness. Dotti *et al.*[53] reported three cases with optic atrophy. Patients are initially floppy and later ataxic. Cerebellar atrophy, particularly involving the vermis,[54] cerebellar dysplasia, arachnoid cyst and absent septum pellucidum[52] have been reported. Zimmer *et al.*[55] reported pathological changes in the muscles with neurogenic atrophy, vacuolar degeneration and non-specific abnormalities of fibre size and mitochondria. They also noted increased lysosomes in conjunctival fibroblasts. Sasaki *et al.*[56] described both rimmed and autophagic vacuoles with numerous myeloid bodies, and a unique dense membrane structure associated with nuclei seen on electron microscopy.

III. Congenital cataract and microcephaly

1. Cerebro-oculo-facio-skeletal syndrome (COFS)

This autosomal recessive syndrome was described by Pena *et al.*[57] and though it may present in different forms[58] it should be suspected in infants presenting with microcephaly, congenital cataracts[59,60] joint contractures and failure to thrive. There is a high incidence of early death, few affected individuals surviving beyond 3 years of age. The characteristic facial features include a prominent nasal root, micrognathia, deep-set microphthalmic eyes and a forehead that slopes sharply backwards (Fig. 4). Other features include blepharophimosis, apparently large pinnae, overlapping upper lip, long philtrum, kyphosis, campylodactyly, rocker-bottom feet (Fig. 4) and a longitudinal plantar

groove. The condition is probably heterogeneous, and is most likely synonymous with early-onset Cockayne syndrome.[61–63]

2. Autosomal recessive congenital infection-like syndrome

This autosomal recessive congenital infection-like syndrome is characterised by microcephaly, intracranial calcification and central nervous system (CNS) disease including seizures (beginning in the first 6 months of life) and hypertonia, in the presence of normal serological screening for congenital infection.[64–67]

Other features that have been reported in this syndrome are hydrocephalus internus, lissencephaly, polymicrogyria,[64,66] dysmorphic features including micognathia,[66,68] microphthalmia,[68] corneal clouding,[66] large ears,[67] prominent nose with anteverted nostrils and prominent occiput.[68] Congenital cataracts noted on the second day of life, and requiring lensectomy, have been reported in a male child with this condition.[68] This syndrome has only been reported in 17 cases, and should not be diagnosed without first excluding congenital infection, as both congenital rubella syndrome[69–73] and congenital varicella syndrome,[74–76] may also result in congenital cataract with microcephaly and CNS anomalies.

3. Autosomal dominant microcephaly, eye anomalies (cataract, coloboma), short stature and mental retardation[77]

4. Autosomal recessive microcephaly, cataract, mental retardation, motor, sensory and autonomic neuropathy[78]

5. Early-onset Cockayne syndrome

The classical Cockayne syndrome is a progressive neurological disorder which becomes manifest in infancy, and is characterised by sun-sensitivity, resulting in bullae and desquamation of the skin, a typical facial appearance which becomes noticeable at about 3–4 years, and later a pigmentary retinopathy. It is due to a slow recovery of DNA and RNA synthesis following exposure to UV light.

The severe early-onset form of the disease is very similar to cerebro-oculo-facio-skeletal (COFS) syndrome,[61] and the diagnosis should be considered in infants presenting with microcephaly, cataracts and joint contractures.[62] There is often early death, or severe failure to thrive. The facial appearance is characteristic with a prominant nasal root and sloping forehead, micrognathia and microphthalmos. Studies of the effects of UV irradiation on cultured fibroblasts from patients with early-onset Cockayne syndrome have shown similar levels of inhibition of RNA synthesis to those seen in Cockayne syndrome;[61] however there have been no cellular studies with UV irradiation performed on patients with COFS syndrome. The phenotypic overlap between early-onset Cockayne syndrome and COFS syndrome suggests that these two conditions may in fact be the same disorder.

6. Cri du chat syndrome (5p deletion)

This syndrome is associated with a partial deletion of the short arm of chromosome 5 in the area of p14 to p15.1. It is characterised by a high shrill cry, microcephaly, hypertelorism, a round face, and marked somatic and mental retardation. Facial features include antimongoloid slant of the palpebral fissures, epicanthic folds, anteverted pinnae, preauricular skin tags, prominent nasal bridge and micrognathia. The cry is not pathognomonic, is not necessary to make the diagnosis, and usually changes in pitch or disappears during infancy. Patients have muscular hypotony, congenital heart and genitourinary defects. Congenital cataracts have been reported in cri du chat syndrome,[79–82] as has microspherophakia.[82] Niebuhr[81] reviewed the findings in 133 reported cases of cri du chat syndrome, and found 6 cases with congenital cataract. These figures may be misrepresentative of the true prevalence of cataract in this group of patients as not all were specifically examined for cataract.

7. Autosomal recessive microcephaly, congenital cataract, renal tubular necrosis and encephalopathy with epilepsy[83]

8. Czeizel-Lowry syndrome: bilateral infantile cataracts, microcephaly with CT changes, mental retardation and Perthes-like hip changes[84]

9. Edwards syndrome: aniridia with cataracts, microphthalmos, microcephaly, choanal atresia, small jaw and bulbous nose[85,86]

10. Autosomal recessive sutural cataracts, retinitis pigmentosa, microcephaly and mental retardation[87]

11. Autosomal recessive microcephaly, congenital cataracts, kyphoscoliosis, failure to thrive and hip dysplasia[88]

12. Autosomal recessive micocephaly, microcornea, congenital cataract, mental retardation, optic atrophy, hypogenitalism, agenesis of the corpus callosum, hypertrichosis and beaked nose[89]

13. Microcephaly, microphthalmia, cataracts, hypogenitalism, mental and growth retardation and dysmorphism[90]

14. Autosomal recessive ataxia, microcephaly, congenital cataract and mental retardation[91]

IV. Congenital cataract and digital abnormalities

1. Majewski syndrome

The features of this lethal syndrome include neonatal dwarfism, short rib-polydactyly, midline cleft of the upper lip and anomalies of the epiglottis. The pelvic and long bones are relatively normal, but the tibiae have a characteristic oval shape. Affected infants may also have ambiguous genitalia and do not survive the neonatal period. The polydactyly involving the fingers may be either pre- or post-axial, whereas when the toes are involved the polydactyly is post-axial. There has been one reported case of congenital cataract in Majewski syndrome;[92] the cataract was nuclear.

2. Smith-Lemli-Opitz syndrome

See above.

3. Congenital cataract, mental retardation, obesity, hypogenitalism, skull deformities and polydactyly

Schachat and Maumenee[93] described a 32-month-old boy with congenital cataract, mental retardation, obesity, hypogenitalism, polydactyly and skull deformities that included multiple Wormian bones and severely defective skull ossification. The authors felt that this probable autosomal recessive syndrome was distinct from Bardet-Biedl syndrome.

V. Congenital cataract and dermatological disease

1. Conradi's syndrome

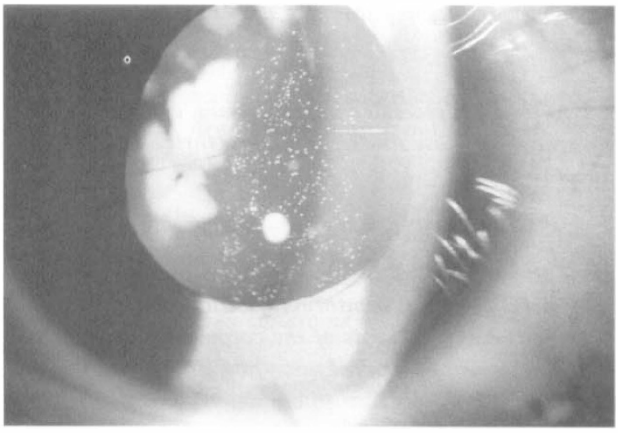
This condition, also known as Conradi–Hunermann syndrome, may be a form of chondrodysplasia punctata. It has been postulated that there are both autosomal and X-linked forms of chondrodysplasia punctata, but this entity usually refers to the X-linked dominant form; Happle[43] has suggested that this form is identical to the proposed autosomal dominant form. Clinically it is difficult to distinguish the two and convincing male-to-male transmission has not been reported. There is an asymmetric shortening of bones and patchy skin changes, which are termed follicular atrophoderma, and clinically either resemble the pitted skin of an orange or appear as patches of dry, scaly skin. On the scalp there are areas of alopecia and the hair is generally sparse and coarse. The main eye signs are cataracts[43] (Fig. 5) and, occasionally, optic atrophy. Radiologically there are multiple areas of punctate calcification at the epiphyseal centres but extra-cartilaginous areas might also be involved.

2. Pollitt syndrome

Pollitt syndrome, also known as Tay, BIDS, IBIDS or PIBIDS syndrome, is characterised by brittle hair with a low sulphur content and the morphological features of trichorhexis nodosa, short stature, mental retardation and sometimes ichthyosis.[94] Osteopetrosis, hypogonadism and cataracts,[95] including congenital cataracts,[96] have been reported. There may be CNS involvement with partial agenesis of the corpus callosum[97] or dysmyelination.[98]

3. Menke's disease

Menke's disease is an X-linked recessive disorder characterised by severe mental retardation, kinky hair, bone and connective tissue lesions, hypothermia and low concentrations of plasma copper and ceruloplasmin. It is caused by a defect of copper transport and metabolism. Onset may be in infancy with lethargy, abnormal temperature regulation, abnormal tone and seizures. The face of an affected individual tends to be pale with full cheeks, tangled eyebrows and a pronounced cupid's bow to the upper lip. The hair may be normal at birth but becomes depigmented, thin and brittle. Neurological deterioration is progressive and death occurs before the



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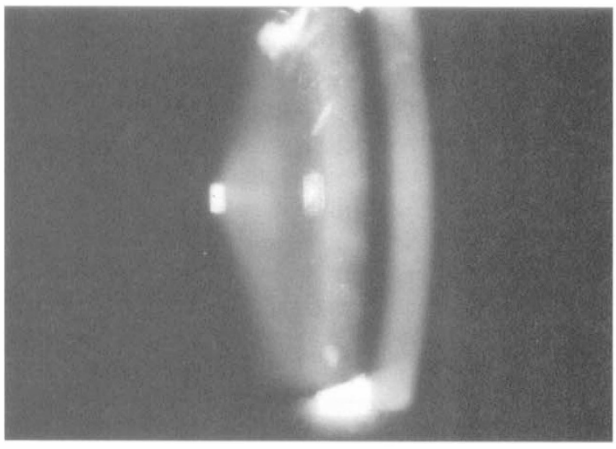

(b)

Fig. 5. *(a) Congenital cataract in a patient with Conradi's syndrome. The opacities are patchy, which may be indicative of X chromosome deactivation. (b) Mother of a patient with Conradi's syndrome.*

age of 3 years. The gene maps to Xq13. Sakano *et al.*[99] reported two cases of Menke's syndrome with bilateral congenital cataracts.

4. Hypertrichosis and congenital cataract

Temtamy and Sinbawy[100] reported an Egyptian brother and sister, the offspring of first cousins, with mental retardation, cataracts, generalised hypertrichosis, microdontia and pectus excavatum.

5. Alopecia, hyperkeratosis and congenital cataract

Wallis *et al.*[101] described an autosomal recessive ectodermal dysplasia in three adult sisters and two brothers from the island of Rodrigues in the Indian Ocean. They had complete alopecia, congenital cataracts, hyperkeratosis of the palms and soles, dystrophic nails and thickening of the skin of the fingers leading to contractures, distal tapering and 'pseudoainhum' formation. All five siblings had normal intelligence.

VI. Congenital cataract with hydrocephalus or skull deformities

1. HEC syndrome: hydrocephalus, endocardial fibroelastosis, cataract

Devi *et al.*[102] reported two unrelated male infants with communicating hydrocephalus, endocardial fibroelastosis and congenital cataracts. Both children died at 4 months of age.

2. Craniosynostosis and congenital cataracts

Lerone *et al.*[103] described congenital cataract together with a severe craniosynostosis, with coronal metopic and sagittal fusion, bilateral nuclear cataracts and a bifid tip of nose in the female offspring of non-consanguineous parents.

3. Martsolf's syndrome

Martsolf *et al.*[104] described two brothers with severe mental retardation, short stature, hypogonadism, cataracts and craniofacial abnormalities, including pouting lower lips, flat malar areas and relative prognathism. They were the offspring of consanguineous parents of Polish Jewish extraction. Other features of the condition are microcephaly, brachycephaly, a flat maxilla, a flat broad sternum, lax finger joints and talipes equinovalgus. The cataracts may be congenital[105,106] or juvenile.[107]

4. Hydrocephalus, congenital cataract and microphthalmia

Cennamo *et al.*[108] described a female infant with hydrocephalus, bilateral congenital cataract and microphthalmia. She was the offspring of consanguineous parents, had a negative TORCH screen, normal chromosomes and no metabolic disorder. A male sibling with hydrocephalus had died a few hours after birth; he was not examined by an ophthalmologist.

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