Ocular Manifestations of Systemic Syndromes

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Arcot Sadagopan Karthikeyan and Adele S. Schneider

Introduction

A syndrome is defined by a group of signs that consistently occur together usually due to a common genetic cause. Syndromes may also be described in response to environmental exposures (e.g. valproate embryopathy) but this chapter focuses only on those with a genetic etiology. The eye is the second most common individual organ to be involved in genetic disorders after brain [1]. Ophthalmic examination is integral in the evaluation of many syndromes. Some ocular manifestations are very specific for a syndrome and greatly assist in making the right diagnosis, as in the chorioretinal lacunae in Aicardi syndrome. Some ocular findings are non-specific such as myopia, strabismus and nasolacrimal duct obstruction. Some syndromes develop ocular manifestations years before systemic signs develop and may have major implications in modifying patient care.

This chapter discusses the ocular and systemic manifestations of syndromes not otherwise covered in chapters on metabolic disorders, chromosomal aberrations, neurologic and mitochondrial disease, craniosynostosis, and phakomatoses or those syndrome with a single predominate systemic manifestation that would cause them to be covered in the chapter related specifically to that system. At the end of the chapter we provide a list of other important texts; atlases and dedicated websites which will assist the reader in making a correct diagnosis and also in recognition and understanding the multitude of syndromes now known.

A.S. Karthikeyan, D.N.B., F.R.C.S. (✉)
Pediatric Ophthalmology, Strabismus and Ocular Genetics, CMER (Shenzhen) Dennis Lam Eye Hospital, 1-2/F, Shengtang Building, No. 1 Tairan 9th Road, Chegongmiao, Futian District, Shenzhen (Intersection of Binhe Road and Tarain Road, Xiasha Station), Shenzhen, China

Pediatric Ophthalmology and Ocular Genetics, Aravind Eye Care System, Madurai, Tamil Nadu, India

Lumbini Eye Institute, Shree Rana Ambika Shah Eye Hospital, Siddharthanagar, Nepal
e-mail: draskarthikeyan@gmail.com

A.S. Schneider, M.D., F.A.C.M.G.
Jefferson Medical College, Philadelphia, PA, USA

Genetics Division, Einstein Medical Center Philadelphia, 5501 Old York Road, Philadelphia, PA 19141, USA
e-mail: schneida@einstein.edu

Adams-Oliver Syndrome (AOS) (MIM 100300)

Definition

Adams-Oliver syndrome (AOS), (MIM 100300) is characterized by congenital absence of skin usually limited to the scalp (Aplasia Cutis Congenita [ACC]) and variable degrees of terminal transverse limb defects. The clinical features are highly variable. Five subtypes (AOS1, AOS2, AOS3, AOS4 and AOS5) have been recognized based on inheritance pattern and the genes involved. Variability in clinical expression has been described with some of the patients with AOS having only ACC and heart defects without associated limb defects [2, 3].

Autosomal dominant and recessive inheritance patterns have been recognized. AOS1 is caused by heterozygous mutations in Rho GTPase activating protein 31 (*ARHGAP31* [MIM 61091]), AOS3 is caused due to heterozygous mutations in recombination signal binding protein for immunoglobulin kappa J region (*RBPJ* [MIM 147183]), homozygous or biallelic mutations in either dedicator of cytokinesis 6 (*DOCK6* causes AOS2 [MIM 614194]). Mutations in EGF-domain-specific O-linked N-acetylglucosamine transferase (*EOGT*) cause AOS4. Mutations in *NOTCH1* (190198) cause AOS5, were identified recently in patients with AOS and may be the most common cause of AOS [4]. Several theories have been postulated to explain the pathogenesis of the observed defects seen in AOS. Early embryonic vascular disruption or insufficiency is considered to the most plausible mechanism [5]. AOS is considered to result from ischemia, necrosis, and resorption of structures after an intrauterine vascular event affecting the brachial artery. This is further

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supported by the occurrence of several vascular malformations and clinical features.

History

In 1945, Adams and Oliver described eight members of one family in three generations with variable defects involving the limb, scalp and skull [6]. Whitley and Gorlin (1991) later reported that another member in the fourth generation was also affected [7].

Epidemiology

Adams-Oliver syndrome is seen in all ethnicities. It is very rare.

Systemic Manifestations

Aplasia Cutis Congenita

The cutaneous defects are usually limited to scalp, mostly midline, sometimes in the occipital or parieto-occipitial area, and can vary in size. Superficial lesions involving only the epidermis are shallow and usually heal over with scarring before the child is born. Deeper lesions usually involve the dermis, subcutaneous tissue or, rarely can involve the skull [8, 9]. In acrania, the flat bones of the cranial vault are absent, whereas the bones at the base of the skull are intact and normal. In some older children, patchy areas of scalp without hair might be the only findings. Dilated scalp veins are frequently an associated finding [10]. Cutaneous defects may also occur on other areas including the face, trunk or limbs. Cutis marmorata might be seen in some of the patients [11, 12]. In some cases maternal serum AFP will be elevated if enough skin is exposed.

Limb Defects

The lower limbs are generally more commonly and also more severely affected [13]. Asymmetrical limb defects are characteristic and seen in approximately 80–85 % of patients with AOS [14]. Hypoplastic or absent distal phalanges are the most commonly reported limb anomalies (see Fig. 21.1). The severity of the spectrum might vary from hypoplastic nails to absence of entire hands or lower legs. Brachydactyly, ectrodactyly, syndactylies are other abnormalities that have been reported [15].

Neurological Manifestations

Neurological abnormalities include encephalocele (uncommon), intellectual disability (uncommon), seizures, hypotonia, developmental delay, enlarged ventricles, periventricular calcifications, cerebral hemorrhage and/or periventricular leukomalacia (PVL). PVL may be due to vascular disruption and decreased perfusion during critical periods of fetal brain development [16]. Neuronal migration abnormalities such as cortical dysplasia, pachygyria and polymicrogyria have also been reported [17]. Hypoplasia of the corpus callosum has been reported [18]. Absence of the superior sagittal sinus also supports the theory of embryonic vascular disruption in the pathogenesis of this syndrome [19–22].

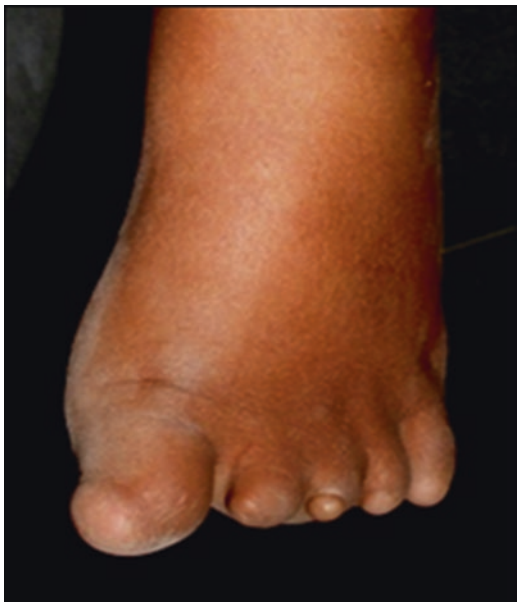

Fig. 21.1 Adams-Oliver syndrome. Terminal transverse limb defect in AOS: The toes are reduced to stubs (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Cardiac Abnormalities

Santos et al. first suggested that cardiac abnormalities could be a part of this syndrome [23]. Approximately 10–20 % individuals with this syndrome might have congenital heart anomalies, mostly involving obstructive lesions on the left side of the heart [24]. Other cardiovascular malformations such as bicuspid aortic valve,[24] atrial septal defect, Shone's complex, aortic valve stenosis, hypoplastic left heart syndrome, double outlet right ventricle, coarctation of aorta [23], ventricular septal defect [25, 26] and tetralogy of Fallot have been reported [3]. Portal hypertension and pulmonary hypertension may occur [2, 27].

Other Abnormalities

The following less consistent abnormalities have also been reported: oligohydramnios, upper limb micromelia, palatal or auricular malformations, anatomic bronchial anomalies, renal anomalies and craniofacial anomalies with frontonasal cysts [28].

Other findings include cutis marmorata telangiectasia congenita (CMTC), abnormal pulmonary and portal vasculature, and necrosis of the abdominal skin and gangrene of digits and optic disc drusen. Several theories have been postulated to explain the pathogenesis of the observed defects seen in AOS. Early embryonic vascular disruption or insuf-

ficiency is considered to the most plausible mechanism [5]. AOS is considered to result from ischemia, necrosis, and resorption of structures after an intrauterine vascular event affecting the brachial artery. This is further supported by the occurrence of several vascular malformations and clinical features.

Ophthalmic Manifestations

Hypertelorism, narrow palpebral fissures, blue sclera, strabismus, microphthalmia, nuclear and anterior polar congenital cataract, retinal dystrophy, congenital vitreoretinal abnormalities, optic disc drusen and congenital optic atrophy have been reported uncommonly [29, 30]. Peripheral avascular retina with capillary dropout, arteriovenous anastomosis, and telangiectasia has been observed [31]. Microphthalmia, microcornea and partial scleralization of the cornea were reported in the other eye. Congenital retinal non-attachment and falciform fold have also been reported [18]. Eyes with optic disc drusen often tend to show abnormal angiogram patterns such as abnormal branching pattern on the disk, increased capillarity and relatively large blood vessels connecting the superficial and deep disk circulations.

Further literature and postmortem examination findings [32] demonstrating abnormalities in the vascular smooth muscle cells and pericyte coverage of the vasculature associated with vessel dilatation (pericyte absence) or stenosis (pericyte hyper proliferation) have been observed [32].

Diagnosis

There are no specific clinical diagnostic criteria due to the heterogeneity in clinical presentation. Some of the important differential diagnoses include the syndrome of scalp defect and split-hand defect, amniotic band sequence and focal dermal hypoplasia (Goltz suyndrome) and [19] Genetic testing offers the definitive diagnosis, although it is expected that other genes are yet to be identified.

Management

Systemic

The main concerns depend on the severity of the scalp defect. The major concern is an open scalp lesion especially when associated with absent of parts of the skull. The risk for developing sepsis and/or meningitis in such patients is high. If the scalp defect is small, recovery occurs with gradual epithelialization and formation of a hairless atrophic scar [33]. Small bony defects tend to close spontaneously during infancy. Large or multiple scalp defects may require surgical intervention.

Ophthalmological

The management of ophthalmological problems in AOS does not differ significantly from those who do not have this syndrome, except for the increased risk for procedures under anesthesia due to the systemic abnormalities. The role of laser ablation of the avascular peripheral retina is unknown.

Aicardi Syndrome (MIM 304050)

Definition

Aicardi syndrome is characterized by the classic triad of, agenesis of the corpus callosum, distinctive chorioretinal lacunae, and infantile spasms. Aicardi Syndrome is an X-Linked dominant disorder. Invariably it occurs sporadically. It is seen only in females with *in utero* lethality in males. The severity of the clinical features appears to be related to the degree of X inactivation. Mosaic mutations have been suggested as possible cause for the rare phenotype of Aicardi that is seen in males. It may also be seen in males with 47 XXY Karyotype [34, 35]. A possibility that Aicardi syndrome is caused by new mutations on an autosome with gender-limited expression in females is currently being considered.

Major Criteria

The presence of all three classic features is diagnostic for Aicardi syndrome. Some patients may not have all three characteristic features. The presence of at least two major features or additional features strongly suggests the possibility of Aicardi syndrome.

Major Features

- Agenesis of the corpus callosum,
- Distinctive chorioretinal lacunae,
- Infantile spasms

Other main features include

- Cortical malformations (usually polymicrogyria)
- Periventricular and subcortical heterotopia
- Cysts around third ventricle and/or choroid plexus (typically not communicating with the ventricles)
- Optic disc/nerve coloboma or hypoplasia

Supporting Features Include

- Skeletal anomalies: vertebral and rib abnormalities
- Microphthalmia
- EEG which has characteristic asynchronous multifocal epileptiform abnormalities with burst suppression

and dissociation between the two hemispheres ("Split-brain" EEG)
- Gross asymmetry of the cerebral hemispheres
- Vascular malformations or vascular malignancy

History

The syndrome was first described by Aicardi et al. [36], as a neurodevelopmental disorder that affects primarily females [37–39].

Epidemiology

Aicardi syndrome incidence has been estimated to be 1:105,000 to 1:167,000 in the United States and slightly more common in some European countries [40].

Systemic Manifestations

The clinical picture is often dominated by neurological symptoms and signs. Other clinical findings include craniofacial, skeletal, gastrointestinal and dermatological manifestations. Some of these patients are at increased risk for certain tumors and cutaneous malignancies. Patients usually have significant neurologic compromise and developmental delay.

Neurological

Aicardi suggested microcephaly, axial hypotonia, and appendicular hypertonia, hemiparesis and unilateral spasticity, global developmental delay and intellectual disability of varying severity as the main features of the syndrome [41–43]. Seizures dominate the neurological presentation. Seizures tend to develop in the first year of life and most by 3 months old. The seizures initially present as infantile spasms but with time present in different forms, often severe and refractory to medical management. Several neuroimaging findings have been reported. Corpus callosum agenesis is the most consistent and is one of the diagnostic criteria. The next consistent finding is polymicrogyria and cortical heterotopias. Polymicrogyria often involves the frontal and perisylvian regions. The heterotopias are almost always bilateral, asymmetric and most often involve the periventricular area [44, 45]. Opercular abnormalities include widening of the operculum and less commonly under development of the operculum. Intracranial cysts that typically do not communicate with the ventricular cavity are seen. The cyst walls show contrast enhancement on MRI. Posterior fossa abnormalities include superior foliar prominence of the vermis, inferior vermian hypoplasia, dysplastic or hypoplastic cerebellar hemispheres, cerebellar subcortical and/or periventricular heterotopias, enlarged cisterna magna and cerebellar cysts.

Dysmorphic Facial Features

Patients with Aicardi syndrome have characteristic craniofacial features which include posterior plagiocephaly, facial asymmetry, sparse eyebrows, large ears, prominent premaxilla, short philtrum and upturned nasal tip. Some of the patients have cleft lip and palate.

Costovertebral Anomalies

Costovertebral abnormalities are common including hemi-, block, and fused vertebrae. Missing ribs are common. Scoliosis is seen in almost one third of the affected individuals [46].

Gastrointestinal

Diarrhea, constipation, Gastroesophageal refluxes are commonly reported symptoms.

Ophthalmic Manifestations

Chorioretinal lacunae are required for the diagnosis of Aicardi syndrome. This clinical finding is highly specific but not pathognomonic. They are usually found in the peripapillary retina or macula. The lesions are white or yellow-white colored, well-circumscribed, round, depigmented areas of the retinal pigment epithelium and underlying choroid. The borders of the lesion often have variable pigmentation. Donnenfeld et al. reported several ophthalmic manifestations including microphthalmia, optic nerve coloboma often usually without co-existent iris coloboma, nystagmus and retinal detachment [46]. Within lacunae, the RPE is typically absent, and the choroid and sclera are thin [47]. The reported eye findings can be unilateral or bilateral and can be grossly asymmetric. Other optic nerve abnormalities include optic nerve aplasia and hypoplasia [47]. Patients also often have cortical visual impairment.

Diagnosis

Diagnosis is based on the diagnostic criteria. Any female infant with seizures early in life needs to have an eye examination to rule-out Aicardi syndrome. Currently there is no specific laboratory, DNA test or diagnostic imaging test to establish a definitive diagnosis. Some of the findings that occur in Aicardi syndrome can also occur in isolation such as agenesis of the corpus callosum and infantile spasm. Parenchymal abnormalities may also be seen in neuronal migration disorders. Some features may share overap with Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation (MCLMR) (OMIM 152950).

Presence of features like agenesis of the corpus callosum with intracranial cysts and other brain abnormalities in a female infant during prenatal ultrasound examination should raise the suspicion for possible Aicardi syndrome. Early ophthalmic fundus examination is critical in all female children with medically refractory seizures to make the correct diagnosis and differentiate it from other causes of seizures in female children and infants.

Management

Systemic

Infantile spasms are often difficult to manage and may be most responsive to vigabatrin. To monitor the side effects of vigabatrin, electroretinogram especially the 30-Hz flicker ERG provides assessment of retinal damage and Ocular Coherence tomography is often required [48].

Ophthalmological

No specific treatment is possible for the chorio-retinal lacunae.

Alagille Syndrome (AGS; MIM 118450)

Definition

Alagille syndrome (AGS; OMIM 118450) is a complex multisystem disorder involving predominantly the liver, heart, eyes, face, and skeleton [49]. It is inherited as an autosomal dominant condition. It is also referred to as Arterohepatic dysplasia.

The diagnosis of AGS is based on clinical criteria initially set forth by Alagille et al. [50]. Which include the histological finding of bile duct paucity on liver biopsy in association with three out of five major clinical features (cholestasis, cardiac defects, vertebral anomalies, ophthalmologic findings, and facial features) and is referred as the classic clinical criteria. Since the association of butterfly vertebrae and cardiac anomalies can be seen in other conditions like chromosome 22q deletion [51], a revised diagnostic criterion has been recently proposed by Kamath et al. [52]. They included presence of typical renal anomaly (renal dysplasia, acidosis, vesico-ureteric reflux and urinary obstruction) as the sixth disease defining criteria.

The majority of cases (97 %) are caused by haploinsufficiency of *JAG1* at 20p11.2-20p12 which encodes the protein (JAGGED1). *JAG1* gene has not been implicated in any other phenotype. It consists of 26 exons, and encodes the JAGGED1 cell surface protein that functions as a ligand for the Notch receptors. There are four receptors Notch 1, 2, 3, and 4. These receptors act as transmembrane proteins, and interaction with their ligands triggers a cascade of intracellular downstream effects that result in transcription of genes. These subsequently help determine cell fate and differentiation. Most of the mutations that involve *JAG1* are protein-truncating. No specific hotspots have been identified, and any part of the entire coding region may be involved. Gene deletions are found in less than 10 % cases. Larger deletions are likely to be associated with additional problems such as learning difficulties. New mutations occur commonly (60 %), and the rate of germline mosaicism may also be relatively high. A small percentage (1 %) is caused by mutations in *NOTCH2*, in which group renal malformations may be more common. Both genes are components of the Notch signaling pathway. *NOTCH2* gene comprises of 34 exons and encodes the *NOTCH2* transmembrane protein. *De novo* mutations contribute to approximately 60 %. Germline mosaicism may occur at a frequency up to 8 % [53]. The current consensus is that AGS is possibly due to a vasculopathy. This is supported by the spectrum of vascular anomalies seen in AGS. There is also evidence that the formation of mature tubular bile ducts follows on from the initial development of the intrahepatic arterial network accounting for the biliary duct atresia.

History

The clinical condition was first reported by Alagille et al. in 1969 [50]. It was subsequently reported by Watson and Miller in 1973 [54], and again by Alagille et al. in 1975. Hence it is sometimes also referred to as Alagille–Watson syndrome.

Epidemiology

The incidence of Alagille syndrome ALGS is estimated to be approximately 1 in 30,000–50,000 live births [55, 56].

Systemic Manifestations

A characteristic inverted triangular face (broad, prominent forehead; pointed chin; bulbous tip of the nose; and deep set, hypertelloric eyes), posterior embryotoxon, cardiovascular defects (particularly peripheral pulmonary artery hypoplasia), and skeletal abnormalities (butterfly vertebrae, shortened ulna and distal phalanges) constitute the main clinical features [57–59].

Facial Features

Recognizing the dysmorphic facial features is critical and one of the major criteria for making a diagnosis [57]. Alagille et al. determined the facial phenotype to be present in 95 % of cases in his series [57]. This was supported in a subsequent

study by Emerick et al. who found the characteristic facial phenotype in 96 % of 92 patients [58]. The characteristic facial features include a prominent forehead, deep-set eyes that may be hyperteloric, straight nose with a flattened tip, and prominent pointed chin.

Sokol et al. suggested that the facial dysmorphism seen in AGS was nonspecific and was secondary to a variety of causes resulting in congenital intrahepatic cholestasis [60]. They referred it to as "cholestasis facies" They suggested that a common structural effect involving several disease genes or the effect of the multiple biochemical aberrations caused by the cholestasis resulted in the facial phenotype. Kamath et al. in their series found that the facial phenotype had 76 % sensitivity and 85 % specificity in making a diagnosis of Alagille syndrome suggesting that the facies seen in Alagille syndrome was very specific to this condition [61]. Hence recognition of the facial features is considered a significant clinical finding and is frequently integral to making the correct diagnosis.

The facial features are more difficult to recognize in adult patients, although recognition of this phenotype in adults has major clinical implications. Individuals might have been followed for apparently isolated congenital heart disease but may be at risk for having severely affected children with full clinical manifestations. The recurrence risk of congenital cardiac abnormalities in children of adults with truly isolated cardiac defects is generally less than 5 % but this risk rises to 50 % in Alagille syndrome [62].

Paucity of bile ducts, which is a histological diagnosis from liver biopsy, occurs in a diverse group of conditions, which, apart from AGS, include Down syndrome, cystic fibrosis, congenital infections, alpha-1-antitrypsin deficiency, and Zellweger and Ivemark syndromes. Screening for characteristic ocular findings may allow early diagnosis and differentiate Alagille syndrome from other causes of intrahepatic cholestasis thus avoiding the need for the extensive and invasive systemic investigations.

Liver

Chronic cholestasis occurs in a very high proportion (95 %) of patients [58]. It often manifests in the first 3 months of life, with jaundice due to conjugated hyperbilirubinaemia. Progressive liver disease eventually resulting in cirrhosis and liver failure require a liver transplantation in approximately 15 % of cases. However a very small proportion of patients do not develop liver disease [49].

Cardiac

More than 90 % have a cardiac abnormality. Involvement of the pulmonary outflow tract in the form of peripheral pulmonic stenosis is the most common finding. Tetralogy of Fallot (TOF) is the most common complex structural anomaly. Congenital heart disease may sometimes be the only manifestation of a mutation in *JAG1*.

Skeletal

A characteristic form of segmentation anomaly known as 'butterfly' vertebrae occurs due to failure of fusion of the anterior vertebral arches. This finding is seen in at least 80 % of cases. These do not have any functional significance but help in making a diagnosis of Alagille syndrome in a child with cardiac disease. Craniosynostosis and radioulnar synostosis have also been reported [63]. Other vertebral anomalies including spina bifida occulta and fusion of adjacent vertebrae, hemi vertebrae, and absence of the 12th rib has been reported. Digits may have shortening of the distal phalanges resulting in fusiform appearance of fingers.

Vascular

Several vascular abnormalities have been reported. Neurovascular accidents, [64], renovascular anomalies, aortic syndrome, and moyamoya syndrome [65, 66] have been reported. Anomalies of the major intracranial blood vessels involving the basilar, carotid, and middle cerebral arteries have also been reported [64, 67]. Intracranial bleeding may occur following trivial head trauma.

They contribute to a significant cause of mortality.

Renal

Structural renal abnormalities include renal dysplasia, small kidneys, renal cysts, and ureter pelvic obstructions. Renal tubular acidosis is the most common functional abnormality reported [52]. Cardiac disease, when severe, accounts for early mortality, whereas hepatic complications account for a significant proportion of later deaths.

Others

Growth retardation and learning difficulties have been reported.

Ophthalmic Manifestations

The most consistent ocular finding is posterior embryotoxon. Other reported anterior segment abnormalities include microcornea, nanophthalmos, keratoconus, band keratopathy, corneal pannus, iris hypoplasia, corectopia, and cataract [68–74, 76, 77]. Refractive errors and strabismus have also been reported [69, 70]. Posterior segment abnormalities include disc and retinal vascular abnormalities [75, 76]. Several optic disc anomalies including tilting, hypoplasia, elevation, atrophy, temporal crescent, peripapillary depigmentation may occur. Optic disc drusen are extremely common and ocular ultrasound has been suggested as a possible noninvasive, simple, and safe method for diagnosis in infants with cholestatic jaundice [78]. Retinal vascular and pigmentary changes, with macular pigment clumping, speckling and chorioretinal folds can occur [70].

Ophthalmic findings are usually mild and most are non-progressive. Hence most patients tend to have reasonably good vision.

Diagnosis

Molecular genetic testing is currently available, although, mutations may not be detected either in *JAG1* and *NOTCH2* in a proportion of the patients.

Alagille must be differentiated from other causes of intrahepatic cholestasis such as cystic fibrosis, congenital infections, alpha-1-antitrypsin deficiency, Zellweger syndrome and Ivemark syndromes. Alagille has a relatively better prognosis for liver disease. The characteristic dysmorphic features, classic ocular findings and specific cardiac abnormalities are not seen in the remaining clinical conditions. Hence it is imperative to look for these findings in any child with neonatal cholestatic jaundice. Several reports suggest examination of the parents alone might provide the diagnosis in at least 36–43 % of cases, and simple ocular examination of the child could reveal a characteristic abnormality in most patients. However posterior embryotoxon is present in 8–15 % of normal persons [79].

Management

Systemic

Multiple specialty services are usually involved. The Kasai procedure, an direct intestine-hepatic anastomosis, is the most common surgical approach to the live malfunction.

Ocular

The retinal pigmentary changes usually do not affect vision.

Alstrom Syndrome (ALMS MIM 203800)

Definition

Alström syndrome is an autosomal recessive genetic disorder characterized by cone-rod dystrophy, hearing loss, childhood truncal obesity, insulin resistance and hyperinsulinemia, type 2 diabetes, hypertriglyceridemia, short stature in adulthood, cardiomyopathy, and progressive pulmonary, hepatic, and renal dysfunction. Symptoms begin to appear even during early infancy and the progressive development of multiorgan pathology results in reduced life expectancy. Though this disorder is unusually frequent among French Acadians, it also occurs in other ethnic groups.

Alström syndrome is caused by bilalellic mutations in the *ALMS1* gene OMIM 203800, located on chromosome 2p13. *ALMS1* is expressed in the organ of Corti, retinal photoreceptors, renal tubules, liver, and pancreatic islets [80, 81]. Several splice variants of *ALMS1* have been described encoding isoforms of the protein accounting for high variability in severity of tissue involvement. Onset of retinal degeneration before age 1 year and occurrence of urologic dysfunction have been linked with disease-causing variants in exon 16 [82]. A more significant association was also found between alterations in exon 8 and absent, mild, or delayed renal disease. There is great variability in age of onset and severity of clinical symptoms, even within family members bearing identical mutations.

The Marshall criteria describe eight major and eight minor clinical features [83]. The recent revised criteria are shown in Table 21.1 [84]. The disorder appears to segregate into three groups: Less than 2 years old, 3–14 years and above 15 years. Presence of two major features is sufficient to make the diagnosis in the first two groups. If only one major criterion is present, the number of additional minor criteria required to make the diagnosis increases with each subsequent age group (2 in group 1, 3 in group 2 and 4 in group 3). The major criteria remain the same for the three age groups. The minor criteria differ in each age group as more systems tend to get affected with disease progression.

Table 21.1 Alstrom syndrome: diagnostic criteria and clincial features

Major criteria (same for all age groups)	
Presence of *ALMS1* mutation in one allele and/or	
Family History of Alstrom Syndrome	
Vision related issues (photophobia/nystagmus/reduced visual acuity/cone dystrophy confirmed by an ERG/legal blindness in adults)	
Minor criteria	
Birth to 2 years	Obesity:
	Dilated Cardiomyopathy/Congestive Heart failure
3 years–14 years	Obesity and/or insulin resistance and/or T2 DM
	History of dilated cardio myopathy/congestive heart failure
	Hearing loss
	Hepatic dysfunction and renal failure
	Advanced bone age
15 years and above	Findings under minor criteria mentioned for age group 3–14 years
	Additional findings include:
	Short stature
	Males: hypogonadism
	Females: irregular menses and/or hyperandrogenism
Supportive findings (common to all age groups)	Recurrent pulmonary and urinary tract infections.
	Developmental delay
	Normal digits
Other findings	Hyperlipidemia, scoliosis, flat feet, hypertension, hypothyroidism, recurrent UTI and alopecia (15 years and above)

History

It was first described by Alström in 1959.

Epidemiology

Alström syndrome appears to have a prevalence of less than one per million in the general population [83]. Patients usually have worsening of all symptoms and signs by second/third decade resulting in reduced life expectancy due to progressive multisystem involvement.

Systemic Manifestations

Obesity

Obesity is one of the early and consistent findings observed in most children with Alström syndrome. They have apparently normal birth weight but gain weight rapidly within the first or second year of life. Decreased levels of physical activity, often exacerbated by dual neurosensory losses and childhood hyperphagia contribute.

Sensorineural Hearing Loss

Hearing loss may be detected in early infancy. It is bilateral and progressive. Most patients have moderate to severe hearing impairment by the second decade [85]. The age of onset and severity is highly variable. Chronic and acute otitis media often exacerbate the sensorineural deficits with a component of conductive hearing loss [83].

Cardiomyopathy

Both dilated cardiomyopathy and restrictive cardiomyopathy has been observed [83, 86]. Dilated cardiomyopathy is more common in early infancy and childhood. It may be the presenting sign of the syndrome. Most children recover but can have a recurrence in later childhood when it presents as restrictive cardiomyopathy. Sixty percent of children with cardiomyopathy develop congestive cardiac failure.

Lung

Chronic bronchitis, asthma, and chronic rhinosinusitis are common. Pulmonary hypertension, Chronic Obstructive Pulmonary Disease and Adult Respiratory Distress Syndrome also occur. History of recurrent hospitalizations for breathlessness is common as some individuals are unable to maintain adequate oxygen saturation.

Type II Diabetes Mellitus

Severe insulin resistance, hyperinsulinemia, and impaired glucose tolerance are often observed from very early childhood. Acanthosis nigricans, a marker of insulin resistance, may occur. The onset of Type II Diabetes Mellitus has been shown to be unrelated to the degree of obesity, unlike the general population [87].

Liver

Elevation of transaminases is common and is often the initial finding. In patients with severe involvement, cirrhosis, portal hypertension, esophageal varices, encephalopathy, with upper gastrointestinal hemorrhage may result in death. End stage liver disease is the cause of death in approximately 10% of individuals [83].

Renal

Renal abnormalities include reduced urine concentrating ability, renal tubular acidosis, polyuria and polydipsia. Secondary hypertencion may occur. Lower urinary tract dysfunction, vesicoureteral reflux, urethral stenosis, and detrusor instability due to abnormal bladder and sphincter function have also been reported [88].

Endocrine

Though there is an initial rapid growth most adolescents and adults have a final short stature. Hypothyroidism and growth hormone deficiency has been reported [89, 90].

Hypogonadism

Hyper- or hypogonadotropic hypogonadism is seen in both males and females. It is more common in males. Secondary sex characteristics are normal. Affected females tend to have hyperandrogenism, hirsutism, and alopecia. No individuals with Alström syndrome are known to have reproduced.

Others

Mild delay in developmental milestones, autistic spectrum behaviors, seizures, and cerebellar anomalies can occur.

Ophthalmic

Progressive cone-rod dystrophy is the main clinical feature. It usually begins in early infancy with parents noticing photophobia, visual impairment and high frequency small amplitude symmetric nystagmus due to early involvement of cones. Full Field-ERG is required to confirm the diagnosis to demonstrate the early cone involvement. When rods get subsequently involved, there is progressive deterioration of vision, constriction of visual fields and eventual blindness usually by third decade. Posterior subcapsular cataracts have been reported. Retinal findings include attenuation of retinal vessels, optic disc pallor, optic nerve drusen and increasingly significant retinal pigmentary epithelial (RPE) atrophy. Histological studies have demonstrated other findings including asteroid hyalosis [91, 92]. The retina may eventually

appear as advanced retinitis puigmentosa. Reports have showed thinning of the macula and an early arrest of macular development with immature retinal structural organization in one of the patients [93]. The severity and age of onset of the retinal degeneration vary among affected individuals [94].

Diagnosis

Molecular genetic testing is available and is one of the major criteria for making a diagnosis.

Since Alström syndrome causes a severe retinal dystrophy with reduced vision and photophobia, it could be confused with several early onset pediatric retinal dystrophies. These include Leber congenital amaurosis (LCA), cone dystrophy and achromatopsia. Often an initial diagnosis of achromatopsia is revised as further characteristic systemic findings emerge. The absence of obesity and other systemic abnormalities, presence of oculodigital sign, enophthalmos and an extinguished ERG response are seen in LCA.

The phenotypic characteristics of Alström syndrome also resemble Bardet-Beidl syndrome (BBS) BBS has polydactyly which is not seen in Alström syndrome. Hearing impairment is less common with BBS. Obesity, insulin resistance and diabetes are common findings in both disorders tend to present slightly at a later age than Alstrom syndrome. Intellectual disability and hypogonadism are more common in BBS.

Other differential diagnoses include Wolfram, Cohen, Biemond II and Usher syndromes. Cohen syndrome has long tapering fingers, a classic facial appearance and high myopia. The presence of diabetes insipidus in addition to diabetes mellitus suggests Wolfram syndrome (also known as DIDMOAD syndrome). The macula is normal in DIDMOAD syndrome. The presence of iris coloboma suggests Biemond syndrome. Obesity is not a feature of Usher syndrome and most of the systemic findings seen in Alstrom syndrome are absent in Usher syndrome. Vestibular abnormalities, as seen in Type 2 Usher syndrome but do not occur in Alström.

Management

Correction of refractive error and vision rehabilitation is required. Given the poor prognosis for vision, early intervention is required. Patients should be screened periodically by echocardiogram to result out emerging cardiomyopathy. Prescription of tinted glasses to avoid photophobia can be attempted. Recommended health care guidelines include

1. Height, weight and BMI
2. Hearing assessment
3. Fasting Blood sugar
4. Serum lipid profile
5. Renal function tests
6. Liver function tests
7. Pediatrician consult
8. Cardiac evaluation by pediatric cardiologist
9. Systemic geneticist consult
10. Endocrinologist consult

Axenfeld-Reiger Spectrum (ARS MIM 180500)

Definition

Axenfeld–Rieger syndrome (ARS) is an autosomal dominant disorder, characterized by anterior segment dysgenesis, dysmorphic facial features and systemic developmental abnormalities. ARS is most often caused by mutations of either *FOXC1* (601090) and *PITX2* (601540). Other genes that have been implicated to have a possible role include *GJA1* [95]. These encode transcription factors which play a critical role in the development of the anterior segment of the eye. The timing of expression and dosage of these transcription factors is critical [96]. Gain of function or haploinsufficiency can result in similar phenotypes [87, 97, 98]. Patients with mutations in *PITX2* are more likely to have systemic abnormalities. An anirdicphenotype can result from 6p25 dosage abnormalities.

History

The clinical condition had been described earlier as several forms initially separated as Axenfeld anomaly, Axenfeld syndrome, Rieger anomaly and Rieger syndrome. It has since been recognized that these phenotypes all fall in a continuum, currently referred as Axenfeld-Rieger spectrum. Axenfeld described posterior embryotoxon with attached iris strands in 1920 [99]. Rieger anomaly was first described by Austrian ophthalmologist, Herweh Rieger, in 1935 [100, 101].

Epidemiology

Axenfeld-Rieger spectrum has an estimated prevalence of 1 in 200,000 people [102].

Systemic Manifestations

Dysmorphic Facial Features

The facies is characterized by subtle craniofacial dysmorphism which includes prominent forehead, broad and flat nasal bridge, mid-facial abnormalities maxillary hypoplasia, hypertelorism and telecanthus.

Dental
Absent teeth, microdontia, delayed eruption, cone shaped teeth and increased spacing between teeth may be seen.

Redundant Periumbilical Skin
Failure of involution of the periumbilical skin in the abdominal region leads to the typical "elephant trunk" umbilicus. Patients also have an increased incidence of umbilical hernia.

Others
Hypospadias in males, pituitary abnormalities, growth retardation and anal stenosis may be observed [103].

Ophthalmic Manifestations

Posterior Embryotoxon
Prominent anteriorly displaced Schwalbe line (the peripheral termination of Descemet's membrane and the anterior limit of the trabeculum) is referred to as posterior embryotoxon [104]. It is seen in 15 % of normal population [105]. It is one of the most consistent findings but not essential to make the diagnosis of ARS. However in the presence of posterior embryotoxon in a child with anterior segment dysgenesis and glaucoma, one should first consider ARS.

Abnormalities of the Iris
Several iris abnormalities can be observed including iris hypoplasia, correctopia and polycoria and most uncommonly, anirdia [106, 107]. Iris processes to the posterior embryotoxonmay or may not be present. Patients with aniridia phenotype do not have the other panocular features of aniridia due to *PAX6* mutation and are not at risk for Wilms tumor.

Glaucoma
Approximately 50 % of the patients develop glaucoma primarily due to the anterior segment dysgenesis [108, 109]. Glaucoma can develop in infancy, but usually tends to occur in adolescence or early adulthood.

Diagnosis

There are no specific diagnostic criteria. If systemic features apart from those discussed above occur, a chromosomal abnormality involving these genes should be suspected or alternative diagnosis considered. Peters anomaly, ICE (Iridocorneal-Endothelial) syndrome, aniridia, congenital ectropion uveae and ectopia lentis etpupillae may mimic ARS. Peter's anomaly is characterized by corneal opacification and variable degrees of irido- or lenticulo-corneal touch. ICE is unilateral and not found in early childhood. True anirdia is associated with foveal hypoplasia, corneal pannus, nystagmus and cataract. Congenital ectropion uveae is unilateral and characterized by prominent ectriopian uvea and a whitish tissue on the iris surface. Ectopia lentis etpupillae has no posterior embryotoxon but also has ectopia lentis in a direction opposite of the corectopia. It may be seen by slit lamp biomicroscopy but gonioscopy is required to detect it in subtle cases [107]. Clinical genetic testing is available. Chromosomal microarray can be useful in identifying the etiology of anirdia like phenotype in such patients in addition to the clinical differentiation discussed.

Management: Recommendations

Systemic
Hearing assessment, systemic genetics consult, dentist consult are required.

Ophthalmic
Patients with ARS have a life time risk of glaucoma and should be monitored. If glaucoma requires surgery, the angle anatomy may make trabeculotomy or goniotomy difficult if not impossible. Periodic monitoring of IOP and disc is critical in all patients with ARS as they have a life time risk of developing glaucoma.

Bardet-Beidl Syndrome (BBS)

Definition

Bardet-Biedl syndrome is an autosomal recessive genetically heterogeneous ciliopathy characterized by retinitis pigmentosa, obesity, renal dysfunction, polydactyly, developmental delay, and hypogonadism. It is one of the more common forms of syndromic RP. It shows very high interfamily and intrafamilial variability. Like most other autosomal recessive disorders, it is more common in highly consanguinous population. It is the first clinical condition where triallelic inheritance characterized by the requirement of 3 mutations in 2 genes to manifest the disease, has been demonstrated.

Bardet-Biedl syndrome can result from mutations in at least 14 different genes. These genes play a critical role in the structure and normal functioning of cilia. *BBS1* accounts for most cases of BBS. *BBS10* is the second most common gene involved. The product of eight genes implicated in the disorder, assemble to form a stable complex called the BBSome. This plays a critical role in signalling receptor trafficking to and from the cilia. Defects in any of the BBS genes eventually affects this complex resulting in ciliopathy and hence BBS. Patient with mutations in *BBS1* tend to be taller [110]. Heterozygous carriers have been shown to have increased risk of obesity, hypertension, diabetes mellitus, renal disease and adenocarcinoma [111, 112].

History

The disorder was previously grouped as one entity along with Lawrence-Moon syndrome as Lawrence-Moon-Bardet-Beidl Syndrome [113]. The first case was reported by Laurence and Moon in 1866. Laurence–Moon syndrome is usually considered a separate entity. Laurence-Moon syndrome is a distinct disorder characterized by the presence of paraplegia and absence of obesity and polydactyly [114].

Epidemiology

The estimated incidence is approximately 1:160,000 in northern European populations and 1:13,500 in some Arab populations [115].

Systemic Manifestations

Dysmorphic Facial Features

The facial features are often subtle and inconsistent: deeply set eyes, hypertelorism, down-slanting palpebral fissures, depressed nasal bridge, small mouth, malar flattening, and retrognathia. Minimal cranial dysmorphic features include brachycephaly, macrocephaly and male frontal balding.

Polydactyly

Polydactyly is seen in approximately 60–80 % of patients [115, 116]. Polydactyly is post-axial and can be seen in upper and/or lower limbs (see Fig. 21.2a–c). It might vary in severity from a small bump to a large complete finger. Other digital anomalies include syndactyly, brachydactyly, and clinodactyly and "sandal-gap" in toes.

Obesity

Patients with BBS usually have normal birth weight [112]. The obesity is truncal in nature and acquired over time. Most patients are obese and often also have associated endocrinological abnormalities. Insulin resistance can be observed and acanthosis nigricans might be seen. Factors contributing to obesity include increased food intake, decreased energy expenditure, reduced physical activity and increased peripheral leptin resistance [117].

Hypogonadism

Hypogonadotropic gonadism is more common in males than in females.

Urogenital

Cryptorchidism and micropenis may also occur. Complex structural urogenital abnormalities can occur in females including partial and complete vaginal atresia, septate vagina, duplication of the uterus, hematocolpos, persistent urogenital sinus, vesico-vaginal fistula, absent vaginal orifice, and absent urethral orifice [118–120]. Hypoplastic fallopian tubes, uterus and ovaries can also occur.

Renal

Both structural and functional abnormalities can occur. Renal manifestations include tubular disease, rare glomerular disease and cystic renal dysplasia [121]. End stage renal failure is one of the causes of morbidity and mortality [121, 122].

Other Features

Developmental delay, speech delay, behavioral abnormalities, brachydactyly, syndactyly, ataxia, diabetes, cardiovascular anomalies, hepatic fibrosis, Hirschsprung disease and anosmia have been reported [123].

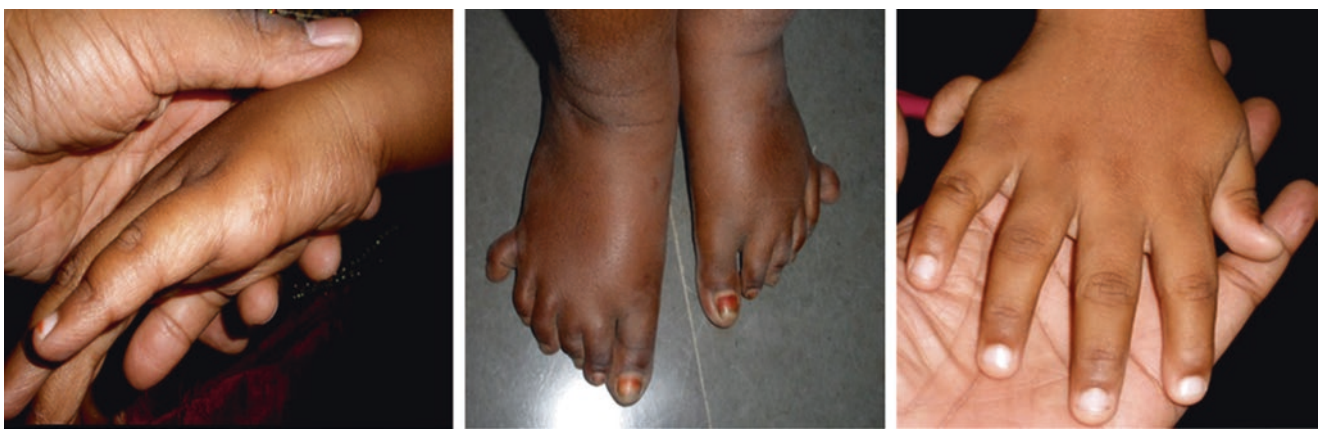

Fig. 21.2 (**a**) Surgical scars following removal of supernumerary post axial polydactyly. (**b**) Photograph of another patient with polydactyly of the foot. (**c**) Photograph of another child with polydactyly (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madura)

Ophthalmic Manifestations

The primary feature is retinal dystrophy. Although it is usually rod-cone, cone-rod phenotypes have also been reported and macular lesions are not uncommon [124]. Retinal dystrophy is observed in 90 % of patients. It usually begins in late childhood and shows typical features of retinitis pigmentosa, but may initially only manifest as internal limiting membrane irregularity and attenuated vessels. Night blindness is the earliest symptom, beginning usually at 7–8 years of age. It is followed by slowly progressive visual field loss. The maculopathy may or may not be associated with peripheral retinal degeneration. There is high inter-familial variability in the onset and severity of symptoms. Other ophthalmic findings include secondary nystagmus, cataract and strabismus as well as primary refractive errors, mainly myopia and astigmatism. Glaucoma is rarely seen.

Diagnosis

A diagnosis can be made based on the presence of four primary clinical features or a combination of three primary features and two secondary features [112].

The primary features include rod-cone dystrophy, polydactyly, truncal obesity, learning disability, hypogonadism and renal anomalies.

The secondary features include developmental delay, speech delay, behavioral abnormalities, and ocular manifestations other than retinal dystrophy like cataract, strabismus and refractive errors, ataxia, hypertonia, endocrine abnormalities like diabetes, cardiac, orodental anomalies and hepatic disease. Hirschsprung disease and anosmia are other secondary features.

Molecular genetic testing can confirm the diagnosis and microarray panel technology for genes known to be involved in BBS is available. There are several clinical conditions which resemble BBS. It is important to carefully observe for surgical scars as many patients would have had a surgical excision at a very young age for cosmetic reasons (see Fig. 21.2a). In the absence of polydactyly it is often difficult to differentiate BBS from many other clinical conditions. However onset of ocular features assists in distinguishing from other clinical conditions. Many patients reported in the literature who were initially diagnosed to have McKusick Kaufmann syndrome were later diagnosed to have BBS when retinal dystrophy became evident. It is currently recommended that all children with a possible diagnosis of McKusick-Kaufman syndrome made during infancy should be re-evaluated for ophthalmological findings and other signs of BBS during follow-up [125].

Differential Diagnosis

McKusick-Kauffman Syndrome (MKS)

It is characterized by the triad of hydrometrocolpos, postaxial polydactyly, and congenital heart disease. It is caused by mutation of *MKKS*, which can also cause BBS accounting for the similar clinical features. MKS is also inherited in an autosomal recessive manner. The main differentiating feature is the absence of retinal dystrophy in MKS.

Meckel-Gruber Syndrome

Meckel-Gruber syndrome, another autosomal recessive condition is usually lethal. It consists of the triad of occipital encephalocele, large polycystic kidneys, and postaxial polydactyly. It is associated with other anomalies that include genital anomalies, central nervous system malformations, and fibrosis of the liver. Pulmonary hypoplasia is the most common cause of death. Mutations in *MKS1* and *TMEM67* can also cause Bardet-Biedl syndrome, thereby demonstrating phenotypic overlap between these two conditions [126, 127].

Alström Syndrome (See Above)

Biemond Syndrome

The presence of ocular coloboma in a child with features with BBS should alert the clinician to this diagnosis. Hydrocephalus and facial dyostosis are additional features.

Cohen Syndrome

This autosomal recessive inherited disorder is characteristised by facial dysmorphism, truncal obesity and retinal dystrophy. There is no polydactyly but the fingers are long and tapering. Some patients also have hyperextensibility of joints. Cerebellar involvement is common and revealed by neuro-imaging. The retinal dystrophy is also different from BBS, and more characterized by pathologic myopia. Transient neutropenia is seen. Intellectual disability tends to be less severe than in BBS. Microcephaly is also a feature.

Management: Recommendations

Systemic

Renal function tests including blood urea and serum creatinine, ultrasound abdomen and pelvis to detect renal and urogenital anomalies is advised. Blood pressure and periodic weight measurement and monitoring should be performed. Developmental assessment, endocrinological evaluation and hearing assessment should be performed. Polydactyly might also cause not only cosmetic concerns but can also cause significant functional limitations in some patients including writing. Pre-axial polydactyly can occur as an isolated genetic disorder or can be seen in other genetic syndromes but is not seen in BBS.

Ophthalmic

Although there is currently no specific treatment for the retinal dystrophy in BBS, a gene therapy trial for one genotype is expected in the near future.

Blepharophimosis Syndrome (BPES MIM 110100)

Definition

Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES; OMIM 110100) is an autosomal dominant syndrome characterized by the presence of four adnexal features: shortened horizontal palpebral fissure length, ptosis, epicanthus inversus, and telecanthus [128]. It has two subtypes. Type I is characterized by the additional finding of primary ovarian failure in affected females. Type 2 does not have ovarian failure. Mutations in the fork head transcription factor gene *FOXL2* have been found to be responsible for BPES. There has been only one report of autosomal recessive transmission in an Indian family [129]. Penetrance appears to be 100 % in BPES1 and 96.5 % in BPES2 [130]. In BPES1 there is transmission by males only as females are infertile. In BPES2, transmission occurs through both sexes. Fifty percent of cases are due to *de novo* mutations. *FOXL2* is the only gene currently known to be associated with BPES. A patient with BPES and genital malformations was reported to have a deletion del(7)(q34) [131]. *FOXL2* gene has a single exon and the encoded protein has an alanine-rich domain. Mutations predicted to result in proteins truncated before the polyalanine tract preferentially lead to BPES1.

Polyalanine expansions preferentially lead to BPES2. Positive correlation between the size of the polyalanine expansion and the penetrance of the BPES phenotype has been reported [129].

Occasionally individuals with BPES may have cytogenetic rearrangements, including interstitial deletions or translocations involving locus interface between 3q22.3 and 3q23 [132] Waardenburg [133] suggested that the ocular defects seen in this syndrome possibly occurred during the third month of intrauterine life as this timing coincides with the critical period in the development of the ovary and the beginning of formation of the uterus by fusion of the Mullerian ducts. It has been shown in mice that the *Foxl2* gene is expressed in the mesenchyme of developing mouse eyelids and adult ovarian follicles [134].

History

Von Ammon' first used the term blepharophimosis in 1841 [135]. However it was Vignes in 1889 that first associated blepharophimosis with ptosis and epicanthus inversus [136].

Epidemiology

The exact frequency of BPES is unknown [137].

Systemic Manifestations

Apart from the primary ovarian failure seen in females affected with BPES1, there are no systemic findings. Secondary sexual characteristics in BPES1 are normal. Intellectual development is usually normal although mild intellectual disability has occasionally been reported and is usually present when a microdeletion is the cause. Large deletions often can cause other associated features like microcephaly, intellectual disability, and growth delay [138–141]. (Balanced translocations involving 3q23 lead to classic BPES without these additional findings.)

Ophthalmic Manifestations

See Fig. 21.3.

Shortened Horizontal Palpebral Fissure Length

The horizontal palpebral fissure length in individuals with BPES usually measures less than 20 mm.

Ptosis

Ptosis is usually severe with poor levator function and present at birth. Patients might use their frontalis muscle in an attempt lift the drooping lid or adopt a compensatory chin up posture. Though the ptosis can cause stimulus deprivation amblyopia or uncorrected refractive error and anisometropia may also contribute.

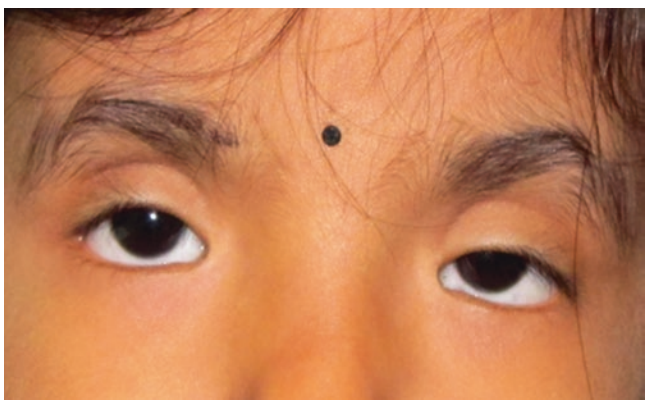

Fig. 21.3 This female child has ptosis, epicanthus inversus, telecanthus and blepharophimosis, the characteristic features of BPES (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Telecanthus

Telecanthus has been reported as the most consistent finding of the syndrome [137]. It is characterized by lateral displacement of the inner canthi with normal interpupillary distance. It may or may not be associated with hypertelorism.

Epicanthus Inversus

BPES is characterized by the presence of epicanthus inversus, where the lower lid contributes to most of the epicanthus and the epicanthal fold extends onto the lower lid below the lashes. Unlike other types of epicanthus, epicanthus inversus does not improve much with age.

Other Eye Abnormalities

Congenital nasolacrimal duct obstruction and strabismus also have a higher incidence in BPES [142]. Hypoplastic supraorbital rims, bushy eyebrows, low set ears and broad nasal bridge are other reported findings particularly in patients with deletions. There is often lateral displacement of the upper and lower lacrimal puncta, more than what would be expected from the lateral displacement of the inner canthi alone.

Diagnosis

BPES is a clinical diagnosis. Molecular genetic testing is currently available.

Chromosomal microarray may be indicated when non ocular features, in particular developmental delay, other than ovarian failure are present. In girls, a positive family history of BPES and infertility can indicate the type of BPES. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation in the family has been identified. There are many syndromes which have either ptosis or blepharophimosis as a feature. In particular, Ohdo syndrome is an X-linked recessive disorder with blepharophimosis, developmental delay and a characteristic facies. Say-Barber syndrome has blepharophimosis, developmental delay, thyroid dysfunction and dental anomalies.,

Management

There is no specific treatment for the primary ovarian failure and infertility in BPES1. Hormone replacement therapy and other reproductive assisted options are available.

Systemic

Females with BPES should be evaluated for primary ovarian failure.

Ophthalmological

The usual approach to this condition is surgical. Medial canthoplasty, for example the Roveda procedure, is often done first at which time correction of the epicanthus may also be accomplished. Ptosis surgery is sometimes performed as the last procedur unless earlier intervention for amblyopia is needed. Levator sling operations tend to be the procedure of choice. The last phase of the correction is usually the extension of the lateral canthus.

CHARGE Syndrome (MIM 214800)

Definition

CHARGE syndrome is the mnemonic for *C*oloboma, *H*eart anomaly, Choanal *A*tresia, *R*etardation of growth and/or development, *G*enital and/or urinary anomalies and *E*ar Anomalies and deafness. Not all features need to be present [143].

The diagnostic criteria as described by Blake et al. (1998), which was modified by Amiel et al. (2001) and subsequently by Verloes (2005) is shown in Table 21.2 [144–146]. The major diagnostic characteristics of CHARGE syndrome are the following.

The presence of four major criteria or a combination of three major and three minor criteria is required. The major features are specific to this syndrome while the minor features are not specific and can be observed in other clinical conditions.

CHARGE syndrome is most often caused by heterozygous mutations in the *CDH7* gene [147]. Most patients have *denovo* mutations. Increased paternal age appears to be risk factor [148]. Genetic testing is available on a clinical basis. The gene encodes the chromodomain helicase DNA-binding protein which is essential for the formation of multipotent migratory neural crest cells which subsequently undergo a major transcriptional reprogramming and acquire a broad differentiation potential. These then migrate throughout the body, giving rise to various important structures that include craniofacial bones and cartilages, the peripheral nervous system and cardiac structures.

History

Hall (1979) and Hittner et al. (1979) provided the first descriptions of this syndrome and hence the eponym Hall-Hittner syndrome was suggested, though the simplicity of the acronym CHARGE has withstood the test of time [149, 150].

Table 21.2 CHARGE syndrome: diagnostic criteria and clincial features

Major criteria	
Coloboma	Coloboma of the iris, retina, choroid, disc; microphthalmia
Cranial nerve dysfunction or anomaly	I: hyposmia or anosmia
	VII: facial palsy (unilateral or bilateral)
	VIII: hypoplasia of auditory nerve
	IX/X: swallowing problems with aspiration
Choanal atresia or stenosis	Unilateral/bilateral: bony or membranous atresia/stenosis
CHARGE syndrome ear	External ear anomalies including "snipped off" helix, prominent antihelix that is usually discontinuous with tragus, triangular concha, decreased cartilage.
	Middle ear: ossicular malformations
	Mondini defect of the cochlea
	Temporal bone abnormalities, absent or hypoplastic semicircular canals
Minor criteria	
Dysmorphic facial features	Square face with broad prominent forehead, prominent nasal bridge and columella and a flat midface
Genital hypoplasia	Micropenis, cryptorchidism in Males
	Hypoplastic labia
	Males and females: delayed puberty secondary to hypogonadotropic hypogonadism
Growth retardation	Short stature, with or without growth hormone deficiency
Developmental delay	Delayed milestones, hypotonia
Cardiovascular malformation	Tetralogy of Fallot, AV canal defects, and aortic arch anomalies
Orofacial cleft	Cleft lip and/or palate
Tracheoesophageal fistula	TE Fistula
Occasional Findings	DiGeorge sequence, Omphalocele or umbilical hernia, bony scoliosis or Hemivertebrae, Renal anomalies including dysgenesis, horseshoe/ectopic kidney, hand anomalies including polydactyly, altered palmar flexion creases, atypical split hand/split foot deformity, short webbed neck, sloping shoulders, and nipple anomalies
Typical CHARGE syndrome	4 Major criteria or 3 Major + 3 Minor
Probable/possible CHARGE syndrome	One or two major + several minor features

Epidemiology

CHARGE syndrome occurs in approximately 1 in 8500 to 10,000 individuals [151].

Systemic Manifestations

Dysmorphic Facial Features

CHARGE syndrome is characterized by a square face, flat midface, broad prominent forehead, and prominent nasal bridge and columella.

Heart Defects

Congenital malformations of the heart are seen in 75–85 % of patients. Many forms of congenital cardiac anomalies can occur.

Choanal Atresia

Observed in up to 60 % of patients, the choanal atresia may be membranous or bony, unilateral or bilateral. Bilateral choanal atresia presents as an emergency at birth with acute respiratory distress. Unilateral atresia may present as unilateral rhinorrhea. Choanal stenosis may also be an incomplete manifestation.

Retarded Growth and Development

Growth retardation and developmental delays commonly occur. Feeding difficulties due to coexistent congenital malformations such as orofacial clefts and tracheoesophageal fistula contribute to growth retardation. Both pre- and postnatal growth deficiency is observed, but patients usually have normal birth weight and length.

Genitourinary Anomalies

Cryptorchidism is seen in males and hypogonadotropic hypogonadism occurs in both males and females. Solitary kidney, hydronephrosis, and renal hypoplasia are some of the renal anomalies. They occur in approximately 25–40 % of children [144].

Ear Anomalies and Hearing

At least 80 % of patients have some form of ear anomaly. The abnormalities can involve the inner ear, middle ear and/or outer ear. The external ear is usually short and wide. The ear lobe may be absent. There is a prominent antihelix that is often discontinuous with the tragus, truncated helix and triangular concha. The middle ear may show ossicular malformations. The semicircular canals may be hypoplastic or absent. Mondini defect of the cochlea is a characteristic finding. The hearing loss can be sensorineural, conductive or

mixed and can vary from a mild to profound hearing loss. The presence of facial palsy suggests the presence of hearing impairment [152].

Vestibular Dysfunction

Absence or hypoplasia of the semicircular canals can impair vestibular balance, especially when combined with visual loss.

Cranial Nerve Dysfunction

Hyposmia, unilateral or bilateral facial palsy, hypoplasia of the auditory nerve and problems with swallowing resulting in aspiration are the most common cranial nerve anomalies observed in CHARGE syndrome.

Behaviour Abnormalities

Obsessive-compulsive, aggressive, and self-abusive behavior may be seen [153]. These abnormal behavior patterns are considered as aberrant attempts at communication about pain, unease, or frustration [154].

Hands

The hands may have a characteristic shape with broad palms and with a "hockey-stick" palmar crease, short fingers and small malformed thumbs.

Others

Skeletal anomalies including scoliosis, rib, vertebral anomalies and limb anomalies, dental anomalies, global developmental delay, and gastro-esophageal reflux may be seen in these patients. Prognosis for life is guarded in the presence of bilateral choanal atresia, cardiac abnormalities and teacheo-oesophageal fistula or esophageal atresia [155]. Male gender and central nervous system malformation appear to have adverse prognosis [143].

Ophthalmic Manifestations

Coloboma may be unilateral or bilateral and seen in 80–90 % of the patients. There is often asymmetric involvement. Macular involvement results in poor visual prognosis. The coloboma may also involve the optic nerve or the optic nerve may be dysplastic. Eyes with coloboma are also prone to retinal detachment. The coloboma may involve only the iris or in some patients there might be a fundus coloboma in the absence of an iris coloboma. Microphthalmia when present further reduces the visual prognosis. Isolated iris coloboma does not affect visual acuity.

Diagnosis

The diagnosis is said to be definitive if the patient has all four major criteria or three major and minor criteria each. The diagnosis is probable if the patient has one or two major and many minor criteria.

Differential Diagnosis

22q11.2 Deletion Syndrome

These children have a distinct facial dysmorphism very different from CHARGE syndrome. They also do not have the ear anomalies seen in CHARGE syndrome. Cleft palate in the absence of cleft lip is more common.

VACTERL association (*V*ertebral anomalies, *A*nal atresia, *C*ardiac anomalies, *T*racheoEsophageal fistula or esophageal atresia, *R*enal abnormalities and *L*imb anomalies) shares many minor features of CHARGE syndrome but lack the major clinical findings of CHARGE syndrome. Coloboma is absent.

Other differentials include Kabuki syndrome (distinct dysmorphic face, cleft palate,, persistent fetal fingertip pads) and renal-coloboma syndrome (also known as papillorenal syndrome, with its characteristic vacant optic disc) which has none of the other major features of CHARGE syndrome. The optic nerve "coloboma" seen in this syndrome is not due to failure of closure of the fetal fissure [156]. Burn-McKeown syndrome (oculo-oto-facial dysplasia) is characterized by choanal atresia, hearing loss, cleft lip/palate, cardiac malformation and protruding ears but also has nasal deformity and lower lid coloboma rather than intraocular coloboma [157].

Management

Systemic

The extensive involvement of several systems requires a team management. Anesthesia considerations include the presence of choanal atresia, cleft lip and palate, and possibility of tracheomalacia.

Ophthalmologic

A full dilated ophthalmologic examination by a pediatric ophthalmologist is required to determine the type and extent of the coloboma and to detect and treat refractive errors, strabismus and amblyopia. Cortical vision impairment (CVI) may contribute to the reduced visual acuity. Periodic follow-up examination to screen for retinal detachment is recommended.

Conradi Hünermann-Happle Syndrome: X Linked Dominant Chondrodysplasia Punctata (MIM 302960)

Definition

Chondrodysplasia punctata (CDP) MIM 302960 is a clinically rare and genetically heterogeneous disorder which encompassesa group of several skeletal disorders character-

ized by the presence of abnormal foci of calcification at the epiphyseal plates, causing radiographic stippling. Cutaneous and ocular findings also occur.

The X-linked recessive from of CDP, known as CPDX1 is caused by mutations in the *CPDX1* gene [158]. Autosomal dominant and recessive forms also occur [2]. Maternal vitamin K deficiency especially during early pregnancy and warfarin teratogenicity can cause CDP.

CPDX2 is inherited as an X-linked dominant disorder known as Conradi-Hünermann Happle syndrome and is the most well characterized form. Mutations in the gene encoding the emopamil-binding protein, encoded by the gene CPDX2 have been identified as an underlying cause. The syndrome occurs due to disturbances in the pathway of cholesterol biosynthesis. Increased levels of 8-dehydrocholesterol and 8[9]-cholestenol are found in these patients. These metabolites appear to have a role on the hedgehog proteins and sonic hedgehog pathway. The Hedgehog proteins play a critical role in the development of limb buds and their correct orientation and also in regulating the embryonic patterning [159], Cartilage formation and enchondral growth.

Affected males usually die in-utero. Rarely males with a milder phenotype can be seen they have an additional X chromosome (e.g. XXY) [160]. The gene is located at Xp11.22-p11.23. Variable inactivation of the X chromosome accounts for the variability in the ocular and systemic findings. Therefore, the phenotypic effect of a given mutation cannot be fully predicted. The hallmark of the condition is the punctate stippling of the epiphysis seen in radiographs in children [161, 162]. These findings tend to disappear after normal epiphyseal ossification in children. Hence early diagnosis is critical. Many clinical features resemble other X-linked dominantly inherited conditions.

History

The clinical features of CDPX2 were first described by Happle and hence referred to as Conradi-Hünermann-Happle (CHH) syndrome [163].

Epidemiology

Malou et al. suggested that the incidence could be 1 in 5, 00,000 [164].

Systemic Manifestations

Dysmorphic Facial Features

Mild dysmorphic facial features including frontal bossing, saddle nose and hypertelorism are often observed. The scalp hair, eyebrows and eye lashes are scanty. Patches of cicatricial alopecia and twisted hairs also occur. The scalp hair also appears coarse and dry.

Skeletal

The most characteristic finding is calcific stippling of the epiphyses, particularly seen in the knees. It is most consistent in the first year of life and later disappears. Asymmetric shortening of limbs and bowing of the legs are prominent features. Scoliosis is frequent and can occur even in early infancy. Growth retardation and short stature are often present.

Skin

Icthysoiform eythroderma and collodion membrane formation can sometimes occur. During infancy, scaling and eythroderma in swirls and linear patterns develop along the lines of Blaschko. The ichthyosis tends to improve with age and might be so subtle in adulthood that it can be easily missed.

Other Manifestations

Hearing loss, congenital cardiac defects, cleft palate, brain anomalies and renal anomalies have been reported [165]. The prognosis is generally good if the child survives infancy. Intellect is typically normal and combined with growth retardation gives a false impression that the child is smarter for the age as lay people easily underestimate the age of the affected patient.

Ophthalmic Manifestations

Nearly two-thirds of patients have cataracts at birth [166] (see Fig. 21.4). They are often asymmetric or even unilateral reflecting the variable X inactivation. Other eye abnormalities that have been reported include microphthalmia, nystagmus, glaucoma and optic nerve atrophy [167, 168]. Vitreoretinal abnormalities in the form of unusual vitreoretinal tractional complexes with underlying retinal pigment epithelium disturbance have been reported [169].

Diagnosis

There are no specific diagnostic criteria. It is a clinical diagnosis based on the constellation of clinical findings involving skeletal, ophthalmological and dermatological findings. The radiographic appearance of punctate stippling is highly suggestive of the diagnosis. Plasma sterol analysis of scales from skin lesions, or cultured lymphoblasts or fibroblasts showing increased concentration of 8[9]-cholestenol and 8-dehydrocholesterol strongly support the diagnosis. DNA testing is available.

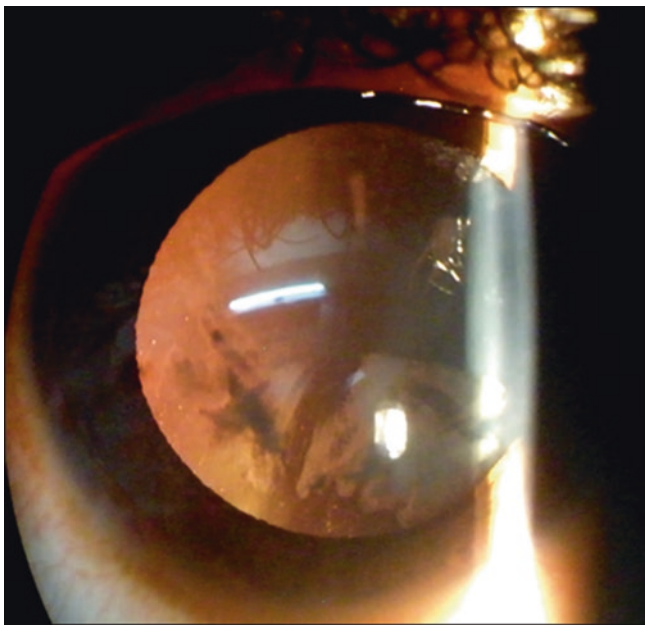

Fig. 21.4 Chondrodysplasia punctata. Partial cataract in a child with X linked Chondrodysplasia punctate (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Management

Systemic

Standard interventions are required for systemic abnormalities like hearing loss, cardiac and renal abnormalities. Orthopedic and dermatological consults should be arranged.

Ophthalmologic

Standard interventions are required for Ophthalmologic abnormalities.

Cockayne Syndrome

Definition

Cockayne syndrome is an autosomal recessive syndrome of premature aging characterized by growth failure, developmental delay, characteristic facies, behavioral and intellectual decline with early mortality and ocular manifestations. There are three subtypes [170]. Type 1 is the classic form and more common than the other subtypes. Type II is the most severe form and manifests prenatally. Type III is a milder form with late onset. The phenotypic spectrum of Cockayne syndrome also includes a fourth condition with overlapping features of Xeroderma pigmentosa and Cockayne syndrome (see Fig. 21.5c). Type I alone has diagnostic criteria. The presence of two major and three minor criteria in an older child is required for making the diagnosis. The presence of two major criteria alone in an infant is sufficient for a diagnosis.

Two major genes are currently known, bilallelic mutations of which cause Cockayne syndrome: excision repair cross-complementation group 6 and Group 8 (*ERCC6* and *ERCC8*). Mutations in other genes *ERCC1* cause Cockayne syndrome type 2 and COFS. Mutations in *ERCC4* cause Type 1. These genes are responsible for making proteins CSB and CSA respectively which actively play a role in repairing defective DNA. *ERCC8* is located at 5q12.1 and *ERCC6* at 10q11.23. There is no specific genotype-phenotype correlation. Mutations in *ERCC6* account for 65% and *ERCC8* account for 35% of the cases with Cockayne syndrome [171, 172]. A mild UV-sensitive syndrome has been reported due to a null mutation of *ERCC6* [173].

DNA is susceptible to damage by ultraviolet rays from the sun and by toxic chemicals, radiation, and free radicals. However normal DNA has the ability to rectify these errors by several repair mechanisms. Mutations in these two genes result in proteins that are unable to participate in some of the repair mechanisms of defective DNA resulting in progressive cumulative errors finally resulting in premature cell death [174]. There appears to be a preferential loss of function to repair active genes [175].

History

Edward Alfred Cockayne first described most of the features of Cockayne syndrome in 1933 [176].

Epidemiology

The incidence of Cockayne syndrome is approximately 2.7 per million births in Western Europe. This disease is probably under diagnosed and under reported [177].

Systemic Manifestations

The systemic features include neurological, dermatological, skeletal, dental and hearing abnormalities. Postnatal severe growth failure and neurological deterioration are the hallmark features. Signs of growth failure occur within the first 2 years of birth in the classic form and are evident at birth in type 2. The neurological findings include hypertonia, hypo or hyper-reflexia, tremor, ataxia and hearing loss. Neuroimaging often shows hypomyelination, supratentorial white matter loss, cerebellar atrophy or hypoplasia. Bilateral putaminal calcifications often occur in classic and

late onset Cockayne syndrome. In addition to these findings cortical calcifications occur more often in earlyonset Cockayne syndrome [178]. A typical stooped posture develops giving the appearance of horse riding stance due to contractures involving the knee joints. Contractures also develop in fingers and toes (see Fig. 21.5b). Dermatological findings include thinning of hair and skin. Cutaneous photosensitivity occurs and is especially more prominent in the variant that has overlapping features of Xeroderma pigmentosa. Dental abnormalities and caries are seen in later childhood. Other manifestations include endocrine abnormalities, renal abnormalities and hepato-splenomegaly [179]. Unlike other disorders that occur due to defective DNA repair, cancers are not common in Cockayne syndrome [180]. The mean age of death is 12 years but survival into the second or third decade has been reported [181]. In the variant with overlapping features with Xeroderma pigmentosa (see Fig. 21.5c), ocular surface neoplasms occur. The prognosis for life is poor with mortality within the first two decades.

Newborns with Type 2 present with severe prenatal growth retardation and then show minimal or no postnatal neurological development. Extensive contractures of the spine and other joints commonly occur. These findings contribute to mortality within the first decade.

Ophthalmic Manifestations

Enophthalmos, microphthalmia, congenital cataract, and miosis often occur [182] (see Fig. 21.5a). Pigmentary retinopathy associated with abnormal electroretinogram is the most consistent and common finding although the retinal exam is limited by miosis [182]. Refractive errors, mainly hyperopia, strabismus and nystagmus also occur [182]. Optic atrophy may occur in isolation or subsequent to pigmentary retinopathy [183]. Corneal opacity and reduced lacrimation have been reported [184]. Corneal perforation has also been reported [183].

Diagnosis

Diagnosis is based on the diagnostic criteria in Type 1. The diagnosis becomes more evident with progression of the condition. The main differential diagnoses include cerebro-oculo-facial syndrome (COFS) is considered as an allelic form of CS, and has overlapping features especially with CS type II and the most severe cases of the CS phenotypic spectrum [185]. Type II shares features with Cerebro-oculo-facial syndrome COFS. DNA testing is available. Other conditions that cause microcephaly and cataract can be differentiated by the sunken eye appearance and retinal dystrophy seen in Cockayne. Congenital infections can simulate Cockayne syndrome due to intracranial calcification. Other disorders due to defective DNA repair such as Blooms syndrome and Xeroderma Pigmentosa and syndromes with premature aging share some clinical features with Cockayne syndrome. Molecular genetic testing is available to confirm the diagnosis (Table 21.3).

Table 21.3 Cockayne syndrome: Diagnostic Criteria and Clinical Features

Major criteria
Postnatal growth failure
Progressive microcephaly and neurologic dysfunction
Minor criteria
Cutaneous photosensitivity with or without thin or dry skin or hair
Demyelinating peripheral neuropathy diagnosed by electromyography, nerve conduction testing, and/or nerve biopsy
Pigmentary retinopathy and/or cataracts
Sensorineural hearing loss
Dental anomalies, including dental caries, enamel hypoplasia, anomalies of tooth number, tooth size and shape
Cachectic dwarfism with thinning of the skin and hair, sunken eyes, and a stooped standing posture
Characteristic radiographic findings of thickening of the calvarium, sclerotic epiphyses, vertebral and pelvic abnormalities
Infants: 2 Major alone is sufficient for diagnosis
In Older children, 2 Major + 3 minor criteria is required for making a diagnosis

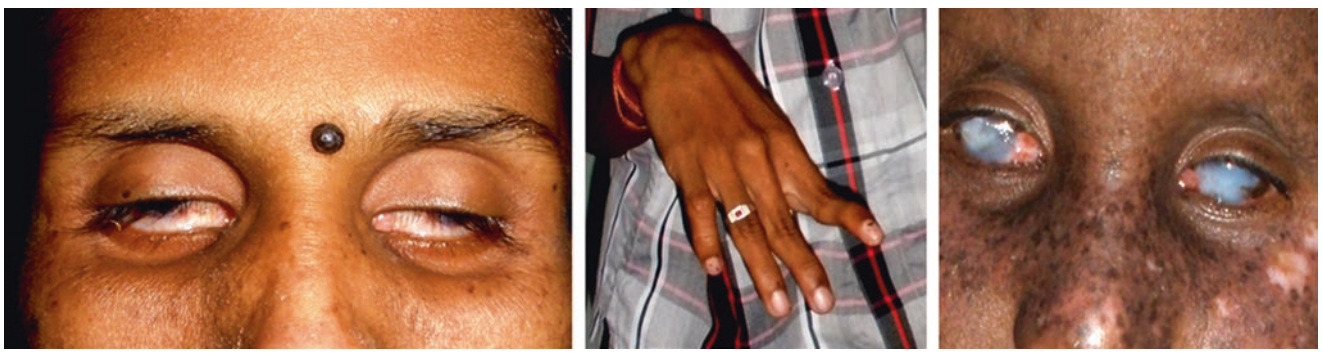

Fig. 21.5 Cockayne syndrome. (**a**) This patient with Cockayne syndrome has deep set eyes (enophthalmos), lagophthalmos and small pupils. She also has cataract. She had retinal dystrophy. (**b**) Contractures are shown in the hand of her sibling, who also was affected with Cockayne syndrome. (**c**) This child has Xeroderma pigmentosa and Cockayne syndrome (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Management

Ophthalmological

Perhaps the most difficult aspect of ophthalmic management is the limitations imposed by the miosis. This may artifactually reduce electroretinogram responsiveness and complicate cataract surgery. Appropriate surgical techniques are required for the latter. Viusal prognosis is poor due to the retinal dystrophy.

Systemic

Monitoring of growth and developmental assessment is necessary. The prognosis for life is poor due to progressive nature of the condition and failure to thrive. Children are at higher risk for anesthesia due to difficulties in airway management and higher risk of gastric aspiration. Laryngeal mask airway appears to be safer than intubation [186, 187].

Cornelia De Lange Syndrome

Definition

Cornelia de Lange Syndrome (CdLS) is a developmental malformation syndrome characterized by short stature, intellectual disability, characteristic dysmorphic facial features, hirsutism, and limb abnormalities. Lifespan may be reduced particularly in more severely affected persons with major malformations but more mildly affected individuals have lived well into their 40s and 50s.

A diagnosis of CdLS is made based on any one of the criteria.

- A disease causing mutation of the genes *NIPBL*, *SMC1A* or *SMC3* by mutation analysis.
- Criteria for facial features + 2 of (growth/development/behavior)
- Criteria for facial features + 3 other criteria (growth/development/behavior + 2 from other category)

The diagnostic criteria is shown in Tables 21.4 and 21.5

Muatations in one of six genes can cause CdLS. All five genes, *NIPBL*, *SMC1A*, *SMC3*, *HDAC8*, *EP300* and *RAD21*, encode components of the cohesion complex. A milder phenotype with characteristic facial features but with less severe cognitive and limb involvement is seen in individuals with mutations in *SMC1A* and *SMC3 NIPBL*, *EP300* and *SMC3*-related CdLS have an autosomal dominant pattern of inheritance. HADC8 and *SMC1A*-related CdLS are X-linked recessive. The *EP300* phenotype tends to be milder. Patients with mutations in HDAC8 have some atypical features including large anterior fontanel, broader nasal root, hooded eyelids and a pleasant personality [188]. Patients with mutations in RAD21 show growth retardation, minor skeletal anomalies and facial features that overlap with typical CdLS. The phenotype is milder [189].

Table 21.4 Cornelia de Lange syndrome: diagnostic criteria and clincial features

CdLS: diagnostic criteria[a]	
A disease causing mutation of the genes *NIPBL*, *SMC1A* or *SMC3* by mutation analysis **OR**	
Criteria for facial features + 2 of (growth/development/behavior) **OR**	
Criteria for facial features + 3 other criteria (growth/development/behavior + 2 from other category)	
Facial features	Eyebrows that meet at the midline and > three or more of the following:
	Long eyelashes
	Short nose, anteverted nostrils
	Long, prominent area between upper lip and nose
	Broad or depressed nasal bridge
	Small or square chin
	Thin lips, downturned corners
	High palate
	Widely spaced or absent teeth
Growth	**(> two or more of the following)**
	Weight below fifth percentile for age
	Height/length below fifth percentile for age
	Head circumference below fifth percentile for age
Development	**(> one or more of the following)**
	Developmental delays or intellectual disability, with speech more affected than motor skills
	Learning disabilities
Behavior	(> two or more of the following)
	Attention deficit disorder plus hyperactivity
	Obsessive-compulsive characteristics
	Anxiety
	Constant roaming
	Aggression
	Self-injurious behavior
	Extreme shyness or withdrawal
	Autistic-like features

[a]Diagnostic criteria for Cornelia de Lange Syndrome (*CdLS*) were created by the CdLS Foundation's Medical Director Antonie Kline, M.D., in collaboration with members of the Clinical Advisory Board of the CdLS Foundation and the Scientific Advisory Committee of the World CdLS Federation

The protein products of the genes appear to play an important role in regulating the structure and organization of chromosomes and are also involved in the repair of damaged DNA. They influence the activity of other genes in the developing limbs, face, and other parts of the body.

History

A German physician Brachmann first described an autopsy of an affected child, but it was Dutch pediatrician Cornelia de Lange who described two surviving children with features

Table 21.5 Cornelia de Lange syndrome: diagnostic criteria and clincial features

Minor criteria
Musculoskeletal (> one or more of the following)
Absent arms or forearms
Three or more of the following or small hands and feet and/or missing digits with two or more of the following
Fifth finger Clinodactyly
Abnormal palmar crease
Dislocated elbow/abnormal elbow extension
Short first knuckle/proximally placed thumb
Bunion
Partial webbing between second and third toes
Scoliosis
Chest or sternum deformity
Hip dislocation or dysplasia
Neurosensory/skin (three or more of the following)
Droopy eyelid(s)
Tear duct malformation or inflammation of eyelid
Nearsightedness
Major eye malformation or peripapillary
Deafness or hearing loss
Seizures
Mottled appearance to skin
Excessive body hair
Small nipples and/or belly button
Other major systems (three or more of the following)
Gastrointestinal malformation/malrotation
Diaphragmatic hernia
Gastroesophageal reflux
Cleft palate or submucous cleft palate
Congenital heart disease
Micropenis
Abnormally placed opening of urethra on penis
Undescended testes
Renal or urinary tract malformation

of this syndrome. The syndrome is sometimes referred to as Brachmann-de Lange syndrome.

Epidemiology

The approximate incidence of this syndrome is 0.6–10 in 100,000.

Systemic Manifestations

Dysmorphism

The dysmorphic features include small or depressed nasal bridge with anteverted nares, small or square chin, long philtrum, thin vermilion border of upper lip, down turned corners of the mouth ("carp shaped"), high arched palate (or cleft palate), micrognathia and small, widely spaced teeth or oligodontia. Patient may show hirsutism as well. Other possible findings include small nipples, small umbilicus and cutis marmorata.

Growth

Weight, head circumference and height are all usually less than fifth percentile both prenatally and after birth. Proportionate short stature occurs. There appears to be a genotype-phenotype correlation between the degree of growth, developmental delay and limb defects [190].

Development and Behavior

A wide range of developmental delays and intellectual disability is seen. There is also a wide spectrum of behavioral patterns including attention deficit disorder, obsessive compulsive disorder, anxiety, aggression, self-injurious behavior and some patients show autistic features. Children are often non verbal even in the presence of normal hearing.

Neurological

Sensorineural hearing loss is seen in 80 % of children with CdLS [191]. Seizures. Some children have a low pitched cry which tends to disappear in late infancy.

Musculoskeletal

Limb reduction defects are a cardinal feature often with oligodactyly, in particular a single digit. In mildly affected children, there is only small hands and feet. Patients with CdLS are also prone to Raynaud phenomena. Clinodactyly, abnormal palmar crease, radial head dislocation, difficulty in elbow extension, short first metacarpal, proximally placed thumb, bunion, partial syndactyly, scoliosis, pectus excavatum and hip dysplasia or dislocation and all been reported.

Gastointestinal

The most common cause of death and also behavioural abnormalties are related to the gastrointestinal tract, in particular gastroesophageal reflux. Other findings include gastrointestinal malformation, and uncommonly, diaphragmatic hernia. Pyloric stenosis is the most frequent cause of persistent vomiting in the newborn period.

Cardiovascular

Approximately 25 % of patients with CdLS have congenital heart disease [192]. Ventricular septal defects, atrial septal defects, pulmonic stenosis, tetralogy of Fallot, hypoplastic left heart syndrome, and bicuspid aortic valve occur in decreasing order of frequency.

Genitourinary

Micropenis, hypospadias, cryptorchidism, genitourinary malformations have been reported [192].

Ophthalmological Manifestations

Synophrys and long eye lashes although not specific, are seen in over 95 % of children with CdLS. A down sloping V-shaped configuration of the eyebrows as they met and extended onto the upper part of the nasal bridge is common. Brow hypertrichosis may be observed. Down-slanting palpebral fissures are less common. Congenital ptosis with poor levator function may be unilateral or bilateral. Severe ptosis was reported to be found among individuals with truncating (nonsense and frame shift) mutations as compared with individuals with missense mutations [193]. Blepahritis with recurrent blepharoconjunctivitis is extremely common and often misdiagnosed as nasolacrimal duct obstruction which is also if high incidence. Other findings include strabismus, nystagmus, and mild microcornea [194]. In almost all children, fundus examination shows a peripapillary pigment ring. High myopia is frequent but retinal detachment may either be due to the myopia or self induced trauma. Less common ophthalmologic abnormalities include glaucoma, cataract astigmatism, optic atrophy, and coloboma of the optic nerve [195–197]. Other findings include ptosis, blepharitis, tear duct malformation, myopia more than 6 D, and peripapillary pigmentation.

Diagnosis

A diagnosis is done based on clinical features and the diagnostic criteria showed in Table 21.6. DNA testing is available as a panel. Fetal alcohol syndrome shares several features with CdLS. Those include intrauterine growth retardation, failure to thrive, developmental abnormalities, microcephaly, facial hirsutism short palpebral apertures, short upturned nose, smooth underdeveloped philtrum, thin upper lip, and cardiac abnormalities. A history of alcohol use during pregnancy provides further clues to the correct diagnosis. Robert syndrome is also a differential diagnosis.

Management

Ophthalmological

Approximately half of these children have a behavioral profile that is characterized by an extreme aversion to touching of their face. This makes glasses, often need for myopia, quite difficult. Contact lens has been successfully used by a few families. The developmental delay may preclude the need for a distant focal point and myopia may even be advantageous. Consideration should be given to examination under anesthesia for identification of treatable peripheral retinal breaks in highly myopic children to prevent retinal detachment. Care during anesthesia is required as some of these patients are predisposed to malignant hyperthermia [198].

Lid hygiene with baby shampoos scrubs has proven to be extremely effective in this patient population in reduction of recurrent blepharoconjunctivitis and also avoiding nasolacrimal duct surgery. It is recommended that trial of this therapy be used in all patients with CdLS prior to nasolacrimal surgery unless there is clearly an anatomic malformation.

Some children have such severe congenital ptosis that there chin lift precludes ambulation. Early surgery, particularly when ambulation may be developmentally expected, can be very beneficial. Levator slings are usually the first procedure.

De Morsier Syndrome (MIM 182230)

Definition

The cardinal feature of De Morsier syndrome is septo-optic dysplasia (SOD), an early forebrain developmental anomaly with ocular and neurological abnormalities. Some reserve the eponym for those children with a characteristic cranoiofacial dysmorphism including broad forehead, typical facies and enlarged anterior fontanelle. SOD is usually characterized by optic nerve hypoplasia, pituitary hormone abnormalities secondary to pituitary hypoplasia and midline brain anomalies including agenesis of the corpus callosum and septum pellucidum. All the three features are present only in 30 % of the patients. The diagnosis of SOD is a clinical diagnosis and can be made if the patient has at least two of the three clinical features. The presence of only one clinical feature is being currently debated to represent a possible milder form of the spectrum of this condition [199]. Other brain findings may include siezures, cortical heteropias and other neuronal migration abnormalities such as schizencephaly.

Current research suggests a combination of genetic and environmental factors in the pathogenesis of SOD. The environmental risk factors that have been proposed include viral infections and specific medications. The disorder is usually autosomal dominant however and may be associated with mutations in *HESX1*. This gene plays a critical role in embryonic development of the eyes, the pituitary gland, and the forebrain. *HESX1* is a paired-like homeobox gene, which acts as a transcriptional repressor and it is one of the earliest markers of murine pituitary development. The frequency of pathological genetic mutations reported so far is very low and mutations have not been identified in many familial cases possibly suggesting the role of new genes. Disruption in blood flow to certain areas of the brain during critical periods of development due to genetic and environmental factors has also been implicated [200, 201].

History

Reeves in 1941 first described this condition as absence of the septum pellucidum in association with optic nerve abnormalities. Association of pituitary abnormality was described subsequently [202]. It is equally common in both sexes and is more common in infants born to younger mothers [203].

Epidemiology

Septo-optic dysplasia has a reported incidence of 1 in 10,000 newborns [204]. It is more common in children born to young mothers. The incidence of true de Morsier syndrome is much lower as SOD can be part of many other syndromes.

Systemic Manifestations

Endocrine

The most common endocrine abnormality is growth hormone deficiency. Thyroid hormone deficiency may occur. Sudden death has been reported due to disruption of the corticosteroid axis [205]. Panhypopituitarism with hypoglycemia, diabetes insipidus, reduced response to thyroid stimulating hormone, and hypogonadotropic hypogonadism can occur. SOD can be associated with precocious puberty secondary to hypothalamic dysfunction, or secondary to LH and FSH deficiency.

Neurologic

Seizures, developmental delay, and cerebral palsy are the most frequent neurologic associations seen with SOD [206]. The classic MRI finding is absence of the pituitary infundibulum and an ectopic posterior pituitary bright spot, often within the stalk. Other associated brain abnormalities include s cavum septum pellucidum, cerebellar hypoplasia, and aplasia of the fornix and Dandy-Walker malformation. Midline brain defects, including agenesis of the septum pellucidum and/or corpus callosum, are present [207].

Other Findings

Other associated findings include obesity, autistic behavior, developmental delays, hearing impairment and temperature instability. Limb malformations have been associated with some patients with SOD and support possible vascular disruption etiology [201]. Adrenal crisis can be precipitated by fever and dehydration due to corticotrophin deficiency resulting in sudden death [205]. Hypothermia and temperature instability also can result in sudden death.

Ophthalmic Manifestations

The characteristic finding is the presence of optic nerve hypoplasia. The hypoplasia is usually bilateral, but can be unilateral or asymmetric. In severe cases, ON aplasia may occur with a globe, but no identifiable optic nerve(s) or chiasm. Unilateral hypoplasia often causes strabismus and bilateral optic nerve hypoplasia may cause nystagmus. The classic hallmark of optic nerve hypoplasia is the presence of the double ring sign. The outer ring corresponds to the junction of the sclera with the lamina cribrosa and the inner ring corresponds to the actual optic nerve [208]. Other ophthalmological findings may include primitive, disorganized or tortuous retinal vascular patterns, foveal hypoplasiaor optioc atrophy. Astigmatism and amblyopia may further compound the visual loss [209]. Occlusion therapy and refractive correction can optimize visual outcomes Visual acuity is difficult to predict based solely on the appearance of the optic nerve. Microphthalmia and other developmental ocular abnormalities may also be seen in combination with features of SOD.

Diagnosis

There are currently no diagnostic criteria. Newborns with hypoplastic optic nerves, hypoglycemia, jaundice, undescended testes, large anterior fontanelles in the absence of increased intracranial pressure, with or without other associated midline abnormalities should raise strong suspicion of the diagnosis of SOD. Clinical ophthalmic examination and neuroimaging greatly assists in arriving at the correct diagnosis. B scan ultrasonography and MRI can be used to demonstrate the small optic nerves although with the latter one must be cautious that the interpretation is not a result of the MRI cut. Careful clinical examination is needed, particularly in mild cases. Identification of anomalous retinal vessel patterns emanating from the optic nerve and an increased distance between the nerve and the fovea may be subtle clues to the presence of optic nerve hypoplasia. When ordering neuroimaging to confirm the diagnosis of SOD, it is important to specifically request adequate cuts of the pituitary gland and its infundibular stalk. Hormonal testing should include thyroid function even if the neonatal screen was reported as normal. Additional hormonal testing can be conducted as indicated. Patterns of restricted growth are worrisome for growth hormone reduction.

Although *HESX1* is available for clinical testing, there are likely other genes involved in the causation of SOD. Multiple syndromes may have optic nerve hypoplasia or SOD as a manifestation. These can be recognized on the basis of other ocular and/or systemic findings. Clinical genetic testing is available for the *HESX1* gene. *OTX2* and *SOX2* mutations

can cause a picture that resembles SOD with an ophthalmia or microphthalmia.

Management

Systemic

Hormonal replacement therapy may be indicated. Ongoing monitoring of growth is essential. The prognosis is better with early diagnosis as hormonal abnormalities can be corrected earlier and risk for hypoglycemia, adrenal crisis can be reduced or avoided.

Ophthlamic

Comprehensive ophthalmic assessment including careful cycloplegic refraction is required. Patching treatment for amblyopia is indicated in unilateral optic nerve hypoplasia.

Joubert Syndrome (Classic) and Its Related Disorders (JSRD)

Definition

Classic Joubert syndrome (JS) is characterized by congenital malformation of the brainstem, in particular cerebellar vermis hypoplasia or aplasia causing a characteristic finding in MRI called the "molar tooth sign" [210]. Patients usually have hypotonia and developmental delay. Dysregulation of breathing results in episodic tachypnea or apnea. Ataxia and ocular abnormalities in the form of atypical movement disorders and retinal dystrophy can occur.

Joubert syndrome and related disorders (JSRD) includes conditions that share the molar tooth sign and the clinical features of classic Joubert syndrome but have other organ system involvement.

The syndrome is genetically very heterogeneous. Currently, 23 genes and several loci have been associated with Joubert syndrome and JSRD. These account only for approximately 50 % of affected patients. Autosomal recessive inheritance is the most common pattern of inheritance. An X linked recessive form due to mutations in *OFD1* also occurs [211]. A digenic pattern of inheritance also has been reported as well [212].

History

The syndrome was first described by Marie Joubert in 1969, in siblings from a large French-Canadian family with intellectual disability, ataxia, abnormal eye movement and agenesis of the cerebellar vermis presenting with episodic tachypnea [213]. The designation for the syndrome was suggested by Boltshauser and Islerin 1977 [214]. The disease defining molar tooth sign was described later [215].

Epidemiology

The prevalence of Joubert syndrome is approximately 1 in 100,000. Many studies suggest that this could be an underestimate [216].

Systemic Manifestations

A spectrum of systemic findings occurs depending upon the involved gene and hence a very thorough systemic examination will greatly assist the clinician in planning appropriate genetic testing (Table 21.6). Some of the systemic manifestations do not have any genotype-phenotype correlations.

Dysmorphism

Dysmorphic facial features include a long face with bitemporal narrowing, high-arched eyebrows, ptosis, prominent nasal bridge with anteverted nostrils, triangular/trapezoid shaped mouth, an open mouth appearance, tongue hypertrophy, prognathism, and low-set ears [217, 218].

Neurologic

The molar tooth sign is the most consistent finding and its presence is critical for making the diagnosis. It is characterized by the appearance of the brain stem in the shape of a molar tooth at the level of junction of midbrain and pons (see Fig. 21.6). The sign comprises an elongated, thick, and mal-oriented superior cerebellar peduncles, deep interpeduncular fossa and cerebellar vermis hypoplasia [219]. This sign has also been demonstrated sometimes by fetal MRI making prenatal diagnosis in some of the patients [220]. Hypotonia, ataxia, developmental delays and intellectual disability occur:intellectual disability can vary from mild to severe but is usually moderate [221]. The presence of ventriculomegaly and/or seizures in a patient with JSRD should prompt testing for CC2D2A-related JS [222].

Respiratory

Episodic apnea and tachypnea can occur in infancy and usually improves with age [219]. Hence birth history regarding apneic and tachypneic spells provides important diagnostic clues in an infant with retinal dystrophy and abnormal ocular movements. The combination of hypotonia, tongue hypertrophy and or obesity often predisposes to obstructive sleep apnea [223].

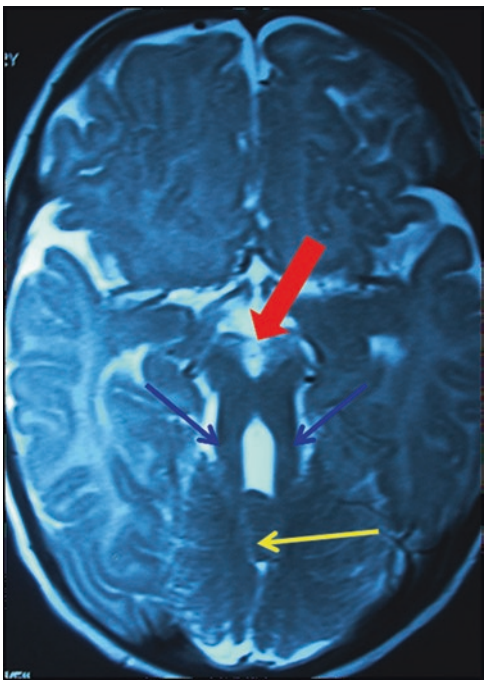

Fig. 21.6 Molar tooth sign in JSRD. Molar tooth sign in Joubert syndrome caused by elongated, thick, and mal-oriented superiorcerebellar peduncles (*blue arrows*), deep interpeduncular fossa (*red arrow*) and cerebellar vermis hypoplasia (*yellow arrow*) (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

Renal

Juvenile nephronophthisis is characterized a chronic tubule-interstitial nephropathy that may progress to end stage renal disease. Cysts can occur at later stages. An adult polycystic kidney disease like phenotype has been linked to mutations in the gene *TMEM67* [224].

Retinal involvement usually has coexistent renal cystic involvement and was referred earlier as Dekaban-Arima syndrome [225].

Hepatic

Some of the patients with JSRD have congenital hepatic fibrosis. These patients also have chorioretinal coloboma and sometimes coexistent renal disease. COACH syndrome is an acronym for coloboma, cognitive impairment ("oligophrenia"), ataxia, cerebellar vermis hypoplasia, and hepatic fibrosis [226].

Ophthalmic Manifestations

Nystagmus

The nystagmus is usually bilateral, conjugate and horizontal. Vertical and torsional nystagmus may occur. A see saw form of nystagmus has also been reported [227]. Pendular nystagmus and gaze-holding nystagmus have been reported [228]. Vestibulo-ocular reflex is present but patients may have poor ability to cancel the vestibulo-ocular reflex horizontally and vertically [215]. Tonic deviation of their eyes laterally and alternating hyperdeviation have also been reported [229].

Oculomotor Apraxia

It is horizontal in nature and might be associated with compensatory head thrusting [227].

Abnormalities occur not only in saccades but also in pursuits [227].

Ptosis

Bilateral and asymmetric ptosis may occur [230].

Ocular Coloboma

The coexistence of fundus coloboma and retinal dystrophy in an infant with oculomotor abnormality should raise the suspicion of JSRD. Iris coloboma may or may not be present.

Retinal Dystrophy

A dystrophic retinal appearance or a frank retinal dystrophy might be seen [227]. Electro retinogram is usually attenuated or might be absent. Visual evoked potential may show asymmetric responses suggesting abnormalities in optic nerve decussation. Optic nerve dysplasia has been reported [215]. Disc coloboma and [230] Optic disc drusen have also been reported [231]. Iris neovascularization has been reported [232].

Diagnosis

The most consistent and obligatory sign that is required for diagnosis is the presence of the molar tooth sign.

A diagnosis of Classic or pure Joubert syndrome is based on the presence of three primary diagnostic criteria.

- Molar tooth sign
- Hypotonia during infancy with later development of ataxia
- Developmental delays or intellectual disability

The molar tooth sign is also noted in disorders that were initially identified as distinct syndromes. These include Senior-Loken syndrome, COACH syndrome, Varadi-Papp syndrome and Dekaban-Arima syndrome [233]. These syndromes now form a spectrum under JSRD [212].

Molar tooth sign may also be found in genetically related disorders like nephronophthisis, Cogan syndrome, Meckel syndrome, MORM, Oral-facial-digital syndrome, Hydrolethalus syndrome, Acrocallosal syndrome (ACLS).

Management Recommendations

Systemic

Periodic monitoring of liver, hepatic function is indicated in the absence of genetic testing. Polysomnography may be required to detect sleep apnea.

Ocular

Ptosis and strabismus are managed as indicated. Refractive errors need attention. There is no specific treatment for oculomotor apraxia.

Lowe Syndrome (OCRL MIM 309000)

Definition

Lowe syndrome (Oculo-cerebro-renal syndrome of Lowe, OCRL) is an X-linked recessive disorder which is characterized by involvement of the eyes, central nervous system and kidneys.

Lowe syndrome is caused by mutations in the *OCRL1* gene at Xq25-q26 which codes for the enzyme inositol polyphosphate 5-phosphatase. There is currently no known genotype-phenotype correlation. Sequence analysis detects mutations in 95 % of males and 95 % of female carriers. Several mutations, including truncation mutations, missense mutations, and large deletions have been reported. *OCRL* plays a role in membrane trafficking.

History

The syndrome was first described in 1952 by Charles Lowe and his colleagues [234].

Epidemiology

The incidence of Lowe syndrome is approximately 1 in 1,000,000 worldwide [235].

Systemic Manifestations

Dysmorphic Facial Features

Facial dysmorphisms are often present and consist in frontal bossing, deep-set eyes, chubby cheeks and a fair complexion [236].

Neurologic

Gross hypotonia is evident at birth. This also contributes to a significant delay in motor development and feeding difficulties. Deep tendon reflexes are often absent. Seizures are common. Intellectual disability and learning disability is seen to some degree in all affected males. Maladaptive behavior is also common including temper tantrums, irritability, stereotypy/mannerisms, obsessions/unusual preoccupations, and negativism [237].

Renal

Proximal tubular dysfunction is the main abnormality (Fanconi syndrome). Fanconi Syndrome is a proximal renal tubular defect which results in loss of potassium, phosphorus, bicarbonate, uric acid, glucose, and amino acid. Loss of bicarbonate results in acidosis. Renal phosphate wasting results in the development of renal rickets, osteomalacia and pathological fractures. Loss of bicarbonate, salt and water results in failure to thrive. Hypercalciuria, leads to nephrocalcinosis and nephrolithiasis can occur. All affected boys have some degree of proteinuria. Chronic renal failure accounts for significant morbidity and results in end stage renal failure. Vitamin D-resistant rickets, amino aciduria (relative sparing of branched amino acids), and reduced ammonia production by the kidney occur. Hypokalemia can occur. Nephrocalcinosis and nephrolithiasis may be a result of the Fanconi syndrome or due to vitamin D therapy for rickets.

Other Manifestations

Gastroesophageal reflux, crytporchidism, inguinal hernia and atelectasis, pneumonia, or chronic lung disease, joint dislocation due to hypermobility, delayed onset of puberty and dental malformations can occur. The most frequent causes of death include respiratory illness, and seizures. Patients often experience failure to thrive and short stature; undescended testis may be seen in up to first/third of patients [238].

Female Carriers of Lowe Syndrome

The clinical findings are highly variable due to the pattern of X inactivation (Lyonization) [239, 240].

Ophthalmic Manifestations

Congenital cataract occurs in all affected male children. They are often dense but begin as posterior polar opacities. Lowe syndrome is one of the few conditions which have coexistent congenital cataract and glaucoma [235]. Other ocular manifestations include microphthalmia, band keratopathy, and corneal keloids or scars. The eyes often appear enophthalmic even in the absence of microphthalmia.

Nystagmus and strabismus are secondary findings. Retinal dysfuction may also be observed [241]. Most carrier females especially post pubertal females tend to have fine irregular, punctate, smooth, radially oriented white to gray opacities in the lens cortex sparing the nucleus. Some of the carriers have snow flake like opacities [242].

Diagnosis

The triad of congenital cataract, hypotonia and renal tubular dysfunction in a male child may be considered as a diagnostic triad. Molecular genetic testing is available on a clinical basis. Enzyme assay in cultured fibroblasts is perhaps the best way to make the diagnosis. In affected males, enzyme levels are usually below 10%. Carrier females often have cataract. Dilated slit-lamp biomicroscopy examination to detect cataract is a highly sensitive test for detection of carriers [243].

Differential diagnosis includes Cystinosis, Nance Horan syndrome, congenital myotonic dystrophy, Smith-Lemli-Opitz syndrome and peroxisomal disorders such as Zellweger syndrome. Nance-Horan syndrome is also an X linked recessive disorder with cataract and dental anoamlies. However they lack the facial appearance of sunken orbits and bitemporal hollowing and the renal abnormalities seen in Lowe syndrome. Peroxisomal disorders are characterized by hypotonia, poor feeding and have distinctive facies different form Lowe syndrome (See under perxosomal disorders). Neonatal seizures are common. Bony stippling (chondrodysplasia punctata) of the patella (e) and other long bones may occur. Other findings that may be seen in older children include retinal dystrophy, sensorineural hearing loss, developmental delay, hypotonia, and liver dysfunction. Renal involvement also assists in differentiating Lowe syndrome from other conditions that cause congenital cataract and hypotonia like peroxisomal disorders, mitochondriopathies or congenital myopathies. Low molecular proteinuria is a consistent and a very sensitive marker for renal involvement. OCRL should be considered in boys with congenital cataracts and glomerular disease, even in the absence of any significant renal tubular abnormality [244]. Dent disease shares several clinical features with Lowe syndrome. Dent disease, also an X linked recessive disorder is characterized by proximal tubule (PT) dysfunction with low-molecular-weight (LMW) proteinuria and hypercalciuria, nephrolithiasis, nephrocalcinosis, and progressive renal failure and is seen only in males. Females are carriers. Mutations in *CLCN5* cause (Dent disease type 1) and mutations in OCRL1 cause (Dent disease type 2). However *CLCN5* gene mutations accounts for most Dent disease. Cataracts and neurologic deficits which are always seen in Lowe syndrome do not occur in Dent disease.

Management

Systemic

Hypotonia causes issues with feeding and nutrition. Associated gastroesophageal reflux further complicates nutrition and development. Renal function monitoring and prevention of development of rickets is essential. As these patients are very susceptible to electrolyte and metabolic imbalance especially during illness, dehydration or stress as in surgery, replacement of fluids, electrolytes and bicarbonate is necessary prior surgery.

Ocular

Cataract surgery is often complicated by the presence of coexisting glaucoma. Children may also need surgical procedures for glaucoma. The glaucoma is often difficult to manage. Visual rehabilitation is usually required and the prognosis is guarded.

Mitochondrial Syndromes

Mitochondria are considered the powerhouse of the cell and are critical for generating ATP by oxidative phosphorylation. Mitochondria have their own genome separate from the nuclear DNA but their function also requires proteins that are encoded by nuclear DNA. Disorders of mitochondrial function can be due to mutations in mitochondrial or nuclear DNA [245]. Only mutations in the mitochondrial genome have the mitochondrial pattern of matrilineal inheritance. Since the sperm does not contribute its mitochondria to the zygote, males do not transmit mitochondrial disease. Affected females can transmit the disease to all of their children, affecting both male and female children (with the exception of Leber hereditary optic neuropathy which is more common in male offspring).

Tissues with higher metabolic rate dependent on oxidative phosphorylation are most often affected including brain, muscles and muscles and hearing [246]. The severity of the phenotype depends upon heteroplasmy [247, 248]. Homoplasmy is the state of having only healthy or only mutated mitochondria while heteroplasmy is the mixed population of normal and mutated mitochondria. The proportion of normal and abnormal mutant mitochondrial DNA in each tissue determines the severity and the threshold (proportion of abnormal mitochondria in each tissue required to manifest disease) for the disease manifestation [249]. Patients should avoid medications that are toxic to mitochondria including aminoglycosides, valproate, fluoxetine, amitriptyline, chlorpromazine, haloperidol, diazepam, and alprazolam.

Other features often seen in most mitochondrial disorders like short stature, hearing loss, dementia, limb weakness, and diabetes mellitus may be seen.

Mitochondrial Encephalopathy, Lactic Acidosis and Stroke Like Episodes (MELAS MIM 540000)

Definition

This genetically heterogeneous disorder has multisystem involvement primarily involving the central nervous system and muscles.

MELAS is caused by mutations in mtDNA and is transmitted by maternal inheritance.

MELAS can result from mutations in any one of several genes, including *MT-ND1*, *MT-ND5*, *MT-TH*, *MT-TL1*, and *MT-TV. MT-TL1* is responsible for most cases [250]. Most of theses genes provide instructions for making transfer RNAs (tRNAs) Genetic counselling is complicated due to heteroplasmy for which the recurrence risk in not consistent even if the mutation is known. Males can be assured that their children will be unaffected. Genetic testing is available on a clinical basis. New *in vitro* fertilization techniques have been developed using a donor egg that has its nucleus removed and replaced by an unaffected donor mother's nucleus. Though it is clear that mitochondrial mutations are responsible for MELAS, the exact mechanism as how these abnormal proteins result in a spectrum of clinical findings is still unclear.

History

It was first described in 1984 [251].

Epidemiology

Mitochondrial diseases occur in about 1 in 4000 people. The exact incidence of MELAS is not known.

Systemic Manifestations

It typically begins during childhood. The symptoms usually begin with generalized tonic-clonic seizures, recurrent headaches, nausea, anorexia, and recurrent vomiting. Stroke like episodes occur following seizures. The episodes may be precipitated by physical exercise and heat. Febrile illness may trigger exacerbations. The severity of clinical manifestations depends upon heteroplasmy, a unique feature of all mitochondrial disorders.

Neurologic

The neurologic findings are usually the first symptoms to appear. These invariably occur in early childhood and almost all patients develop symptoms and signs before the beginning of the fourth decade. Stroke-like episodes are often precipitated by exercise. These "Stroke like episodes" are result of focal cerebral metabolic crisis and bear little resemblance to strokes of an atherosclerotic or thrombo-embolic etiology. This distinction is important to avoid misdiagnosis. Even in the absence of a focal deficit there may be focal EEG and MRI abnormalities. A stroke results in a permanent neurological deficit that persists more than 24 h. In a stroke like episode, the neurological function might fully recover after the episode but the resultant neuronal loss causes a gradual step-wise reduction in cerebral function [252]. Transient hemiparesis and cortical blindness can occur after these episodes. Patients may also develop altered consciousness following these attacks. Many patients develop acute migraine during the stroke. Behavioral abnormalities and autistic behavior may occur [253]. Hearing impairment may occur as a primary manifestation [254]. Myoclonus, learning disability, cerebellar signs, increased CSF protein and basal ganglia calcification are some of the other neurological findings seen [255–257].

Some of the neuroimaging findings are transient, occurring only during the time of stroke-like episodes. MRI often shows increased T2 signal, typically involving the posterior cerebrum and do not conform to the distribution of major arteries. Diffusion-weighted MRI might show increased apparent diffusion coefficient (ADC) in stroke-like lesions. Vasogenic edema and in some patients cytotoxic edema is responsible for the imaging findings. A decrease in N-acetylaspartate and an increase in lactate have been reported in H-magnetic resonance spectroscopy [257].

Ophthalmic Manifestations

Optic atrophy, pigmentary retinopathy and ophthalmoplegia are the common ophthalmic manifestations reported. Abnormal photopic and scotopic ERG can occur. Macular retinal pigment epithelial atrophy may be seen. A reversible, homonymous hemianopia, atypical retinitis pigmentosa with marked attenuation of the scotopic ERG, myopia and nuclear cataract has been reported in MELAS [258]. A clinical presentation of Chronic Progressive external ophthalmoplegia (PEO) with diabetes mellitus (DM), cardiomyopathy and deafness has been reported [259].

Diagnosis

The clinical triad of stroke like episodes, encephalopathy with seizures and dementia, and myopathy with lactic

acidosis and red ragged fibers when present along with any two of the three following clinical features, recurrent headache, recurrent vomiting and normal early psychomotor development confirms the diagnosis of MELAS syndrome. Ragged red fibers on muscle biopsy are often diagnostic. In patients with CPEO, the mutation might be seen only in the muscle tissue and may be missed in other tissues.

Kearns-Sayre Syndrome (MIM 530000)

Definition

Kearns-Sayre is a multisystem disorder predominantly affecting the eyes, central nervous system, skeletal muscle, and heart. It is a form of chronic progressive external ophthalmoplegia. KSS is caused by large deletions of mitochondrial DNA (mtDNA), resulting in the loss of genes involved in the oxidative phosphorylation pathway.

History

This triad of CPEO, bilateral pigmentary retinopathy, and cardiac conduction abnormalities was first described in 1958 by Thomas P. Kearns (1922), MD and George Pomeroy Sayre (1911).

The syndrome was described by Kearns in 9 unrelated patients who had known positive family history [260]. Mitochondrial deletions as a cause of KSS were established in 1988 [261].

Epidemiology

It occurs approximately in 1–3 per 100,000 individuals [262].

Systemic Manifestations

Cardiac

Several cardiac anomalies have been reported. The most serious concern for a patient with KSS is sudden cardiac death due to arrhythmias. Cardiac conduction disturbances are the most common. Atrioventricular block is the most common. Cardiac arrest has also been reported [263]. Also co-inheritance of Long QT syndrome and KSS has been documented [264]. Apart from the conduction disturbances, cardiomyopathy can occur [265].

Endocrine

Many endocrine abnormalities occur including hypoparathyroidism, menstrual abnormalities, growth hormone deficiency and diabetes mellitus occur [266]. Short stature, gonadal failure, hyperaldosteronism, hypomagnesaemia, abnormalities in calcification of bone and tooth has also been reported [267] Mitochondria are a prerequisite for steroidogenesis as well as the secretion and action of insulin [268].

Neurologic

Seizures and strokes are rare in Kearne-Sayre syndrome. Cerebellar ataxia, intellectual deficit, dysarthria, bilateral facial weakness are some of the common neurological findings. Calcification of the basal ganglia has been reported. Cerebellar ataxia, increased CSF protein content cerebrospinal fluid (CSF) protein content above 100 mg/dL are important and one of them is required for making the diagnosis apart from the presence of the characteristic triad. Syncope is a manifestation of cardiac arrhythmia.

Hearing

Sensory neural hearing loss can occur

Ophthalmic Manifestations

Ptosis

This is usually bilateral. Rarely patients might develop external ophthalmoplegia ahead of ptosis and may cause diagnostic confusion. Since these patients have poor bells phenomenon, Crutch glasses are recommended.

External Ophthalmoplegia

It is the most common ocular manifestation of all mitochondrial myopathies. Though there is external ophthalmoplegia, patients usually do not complain of double vision, (even when ptosis does not obscure the visual axis). There is progressive limitation of all movements.

Pigmentary Retinopathy

The most common form of retinal pigmentary retinopathy is salt and pepper retinopathy, which typically becomes more prominent with age [269]. it is one of the diagnostic triads of KSS.

Cataract

Cataract is Less Common

Cornea

Corneal abnormalities are less common but have been reported and can precede systemic findings by several years [270].

Optic Atrophy

This could follow optic neuritis [271].

Diagnosis

It is characterized by the triad of pigmentary retinopathy (salt and pepper retinopathy), progressive external ophthalmoplegia and onset before 20 years old of age. The presence of these three features and at least one of the following is required to make the diagnosis: The other three features include cardiac conduction defects, increased CSF protein and cerebellar ataxia. Other features often seen in most mitochondrial disorders like short stature, hearing loss, dementia, limb weakness, and diabetes mellitus may be seen.

Management

Systemic

Treatment of KSS is supportive. Regular periodic follow-up with a cardiologist is recommended. A permanent pacemaker/implantable cardioverter-defibrillator device has been recommended in those with high-grade heart block. Hearing aids may benefit those with sensorineural deafness. Coenzyme Q10 supplementation has been beneficial in some patients.

Ophthalmologic

Ptosis is best managed with crutch glasses. There is no specific cure currently for the pigmentary retinopathy.

Prognosis

Prognosis for vision and life is poor due to arrhythmias causing sudden cardiac death. Most patients die before the third decade due to heart block. The prognosis for life is better in CPEO than in Kearns-Sayre syndrome.

Myoclonic Epilepsy Associated with Ragged-Red Fibers (MERRF MIM 545000)

Definition

MERRF was first described by Fukuhara et al. [272] is characterized by the presence of myoclonus, generalized epilepsy, ataxia and ragged-red fibers (RRF) in skeletal muscle biopsy. Mitochondrial pattern of inheritance was demonstrated initially in a large family by Rosing et al. [273] Many clinical features overlap with MELAS and some patients initially be diagnosed to have one entity develop clinical features of the other during course of time [274–276]. Mutations in the genes *MT-TK*, *MT-TL1*, *MT-TH*, *MT-TS1*, *MT-TS2*, and *MT-TF* have been recognized to cause MERRF. Mutations result in deficiency of enzyme complexes that actively participate in the respiratory chain especially those involving NADH-CoQ reductase.

History

Shoffner at al first demonstrated mutations in mitochondria as a cause for MERRF [277].

Epidemiology

The exact prevalence of MERFF is not known.

Systemic Manifestations

Neruologic

The neurological features include myoclonus, weakness (myopathy), and spasticity.

Myoclonic epilepsy:

The characteristic feature of MERFF is myoclonic seizures.

Myoclonic seizures are sudden brief jerks or twitching of a muscle or group of muscles and the patient does not lose consciousness.

Myoclonic jerks, epilepsy, ataxia, peripheral neuropathy, and gradual deterioration of intellectual function can occur. Other features that have been reported include generalized tonic-clonic seizures, paroxysmal hearing impairment [276]. Migraine, homonymous hemianopia and hemiparesis have been reported [275] Basal ganglia calcification as seen in many mitochondrial disorders occurs [278].

Red Ragged Fibers

Muscle biopsies show many ragged-red fibers which is consistent with mitochondrial accumulation and shows abnormal mitochondria with concentric cristae. The biopsy also reveals COX deficiency. When muscle is stained with Gomori Trichrome, characteristic ragged-red fibers are visible under the microscope. This appearance is due to the accumulation of abnormal mitochondria below the plasma membrane of the muscle fiber. These may increase and extend throughout the muscle fiber as the severity of the disease increases. The mitochondrial aggregates causing an irregular contour of the muscle fiber and hence the name "ragged" fibers.

Others

Short stature and exercise intolerance is noted. There is an increased trendency for subcutaneous lipoma formation [279].

Ophthalmic Manifestations

Retinal pigmentary changes have been reported [280]. A mild form of ophthalmoparesis was reported [281]. Optic atrophy may also be seen.

Diagnosis

Increased blood and CSF lactate is common. The CSF protein is also increased.

Muscle biopsy typically shows ragged red fibers (RRF) with the modified Gomori trichrome stain and hyperactive fibers with the succinate dehydrogenase (SDH) stain. These RRF do not stain with the histochemical reaction for cytochrome c oxidase (COX). Occasionally, Rarely RRF may not be seen [281].

Molecular genetic testing for involved mitochondrial genes is possible.

Management

Systemic
Aerobic exercises may help in reducing the exercise tolerance.

Ophthalmologic
No specific treatment is available for the ophthalmoparesis or pigmentary retinopathy.

Prognosis

Neuropathy, Ataxia and Retinitis Pigmentosa (NARP) (MIM 551500)

NARP is a mitochondrial disorder characterized by the triad of proximal muscle weakness with sensory neuropathy, ataxia and retinitis pigmentosa. NARP is a progressive neurodegenerative disorder caused due to abnormalities in mitochondrial energy generation.

MT-ATP6 is the only mitochondrial gene in which mutations are known to cause NARP. NARP is almost exclusively associated with the m.8993 T>C/G mutation. Mutation m.8989G>C has been reported recently [282]. Other mutations in MT-ATP 6 are associated with Leigh syndrome or Leber's hereditary optic neuropathy (LHON).

History

NARP was first described by Holt et al. [248].

Epidemiology

The prevalence is approximately 1.9/100,000 [283].

Clinical Manifestations

Systemic

Neurologic
Neurogenic muscle weakness with sensory neuropathy is the main neurological finding. Seizures, learning difficulties, and dementia are other neurological findings [284]. Learning disability, developmental delay and ataxia usually appear early in children prior development of ophthalmological findings and neurological findings. Cerebral and cerebellar atrophy may be observed on MRI.

Ophthalmological
The earliest appearance is a salt and pepper retinopathy. The retinopathy is progressive [285]. Classic fundus findings of retinitis pigmentosa (Pale disc, bone spicules and vascular attenuation) occur with progression of disease. The ophthalmological findings usually appear in the second decade. The fundus findings are highly variable [286]. Electroretinogram (ERG) may reveal reduced amplitudes or may be normal. ERG may show predominantly cone dysfunction in some families and rod dysfunction in others [287]. Visual field loss worsens following retina disease progression.

Other Features
Short Stature, seizures, dementia, sleep apnea, hearing loss and cardiac arrhythmias are other findings that may be seen in NARP. Obstructive sleep apnea has been reported [288].

Diagnosis

The diagnosis is based on clinical findings, the presence of high lactate (more consistent in CSF), ERG abnormalities and Neuroimaging. The diagnosis can be confirmed by molecular genetic testing for mutations in the *MT-ATP6* gene. The main differential diagnosis includes maternally inherited Leigh syndrome (MIL) which may sometimes be caused with increased mutational load in the same 8993 T>C/G NARP mutation.

Management

Systemic
There is no specific treatment for NARP.

Ophthalmologic
There is no specific treatment for ocular findings of NARP.

Prognosis

The quality of life is severely affected as most patients become dependent on others and eventually wheel chair bound.

They share several clinical features common to other mitochondria disorders. However the main features of sensory neuropathy and ataxia are the dominating features. Mutations in the *MT-ATP6* gene cause NARP.

The general evaluation of mitochondrial disorders involves several clinical and biochemical tests. Most mitochondrial disorders require a panel of investigations. They include the following. Blood and CSF lactate and pyruvate levels, cardiac evaluation including echocardiogram and electrocardiogram, fasting glucose and HBA1C concentration to screen for and monitor diabetes mellitus, brain MRI and muscle biopsy are required. The characteristic finding in muscle biopsy is the presence of ragged-red fibers (RRF) with the modified Gomori trichrome stain. They are COX negative. Electromyogram and nerve conduction studies may be required. Biochemical studies of respiratory chain enzymes in muscle extracts may show decreased activities of respiratory chain complexes.

Möebius Syndrome (MIM 157900)

Definition

Möebius syndrome is a congenital complex developmental disorder of the brainstem with non-progressive facial weakness and limited abduction of one (rarely) or both eyes. It is currently recognized as one of the congenital cranial dysinnervation disorders (CCDD).

Möebius syndrome probably results from a combination of environmental and genetic factors.

Most cases of Möebius syndrome are sporadic. Autosomal dominant cases have been reported [289–292]. No specific gene has been identified though several loci have been suggested [289]. Cytogenetic studies in some reports have shown a possible location for the gene responsible for Möebius syndrome to be located at region 13q12.2-q13 [293, 294]. Other reports have suggested a possible location at 1p22 [295, 296]. A patient with an inherited inversion of the sixth chromosome has been reported [297]. Other suggested loci include 3q61 and 10q62 [298]. Recently mutations in *PLXND1* and *REV3L* have been reported in Möebius syndrome [299, 300].

Current research suggests that Möebius syndrome may result from a vascular insult to the brainstem during very early stages of embryonic development. Möebius syndrome is a complex regional developmental disorder of the brainstem. Defects at different levels at supranuclear, nuclear, or peripheral levels in different patients were suggested based on electrophysiological studies [301].

Environmental factors especially certain medications taken during pregnancy (Thalidomide and Misoprostol) and drug abuse like cocaine may also be risk factors for Möebius syndrome. Classic features of Möebius syndrome including involvement of the sixth and seventh cranial nerves, aberrant tearing, and recent observations of autism spectrum disorder (ASD have all been reported due to the teratogen thalidomide). Thought the most frequent eye complication due to thalidomide is Duane syndrome, secondary to damage to the cranial nuclei in the brain stem. Hence this condition probably results from a combination of environmental and genetic factors [302].

The recurrence risk appears to be as low as 2%. The absence of skeletal defects appears to increase the risk of recurrence in the family [300].

Based on neuropathology findings, Towfighi et al. proposed four categories of Möebius syndrome (MIM 157900) [303]

Group I: Hypoplasia of cranial nerve nuclei resulting from congenital rhombomeric maldevelopment
Group II: Neuronal loss and neuronal degeneration secondary to a defect in the facial peripheral nerve
Group III: Decreased neurons as well as degeneration, focal necrosis, gliosis, and calcifications in the brainstem nuclei due to vascular insufficiency or infection
Group IV: Primary myopathic changes without lesions in the cranial nerve nuclei or nerves.

History

Von Graffe first described this condition in 1880 [304]. Möebius subsequently described the features more elaborately in 1888 [305].

Epidemiology

The prevalence rate reported is 1/150,000 of babies born alive [306].

Systemic Manifestations

Neurological Features

A characteristic mask like facies is seen due to bilateral facial nerve palsy. Patients have an inability to smile normally. Micrognathia is common with or without Pierre Robin sequence.

Motor abnormalities and poor co-ordination occur. Cerebellar hypoplasia has been reported [307]. Although most patients have normal intelligence, intellectual and learning disability have been described [308]. Behavioral issues and autistic spectrum disorders may occur [309]. Many cranial nerves including the 3rd, 5th, 8th, 9th, 11th and

12th may be affected. The latter may be manifested by crenulations on the side of an extended tongue or deviation when the tongue is extended. Inability to suck may be one of the earliest symptoms. Other symptoms may include difficulty in swallowing, excessive drooling, and speech difficulty. Verzijl et al. suggested that the unusual distribution of the facial weakness in Möebius syndrome possibly suggests that other cranial nerves, including the trigeminal, hypoglossal, or glossopharyngeal nerve, aberrantly innervate some lower facial muscles [310]. MRI demonstrated absence of facial nerves in those patients [310]. Möebius syndrome is part of a more complex congenital anomaly of the posterior fossa as suggested by radiological evidence [311]. Clinical extension beyond the lower brainstem and cerebellum are common. Neuroimaging may reveal hypoplasia of the brain stem, straightening of the floor of the fourth ventricle and absence of the medial colliculus at the level of the pons. There is hypoplasia of cranial nerve nuclei VI and VII. Some patients might also show absence of the hypoglossal eminence at the medulla [311, 312].

Limb Anomalies

Upper limb anomalies include brachydactyly, clinodactyly, and syndactyly. Lower limb anomalies include pes planus, and talipes equinovarus. Poland syndrome (Unilateral absence or hypoplasia of the pectoralis muscle and variable degree of ipsilateral hand and digit anomalies) [313, 314], may be associated with Möebius syndrome.

Other Findings

Hypogonadotropic gonadism has been reported [315]. It includes several other clinical features: hearing loss, other cranial nerve dysfunction, motor, orofacial hypotonia, musculoskeletal, neurodevelopmental, and social problems.

Ophthalmic Manifestations

Bilateral limitation of abduction is the key ocular motility finding. Most patients are orthotropic but esotropia may occur. Limitation of abduction, esotropia, V-pattern strabismus, and compound hyperopic astigmatism were the prominent findings in one of the studies [308]. Isolated abducens nerve palsy, conjugated horizontal gaze paresis, features of DRS, and congenital fibrosis of the extraocular muscles were reported in a major study [289]. convergence may be poor or absent [316]. Co-existent involvement of supranuclear vergence centres in mid brain has been suggested as a cause for defective convergence [317]. Duane retraction syndrome can occur. Vestibulo-ocular reflexes; however, have previously been reported to be absent horizontally in Möebius syndrome Ocular motility deficits similar to congenital fibrosis of the extraocularmuscles (CFEOM) types 1 and 2 have been reported in Möebius syndrome [318–320]. Lagophthalmos due to bilateral facial palsy occurs although ptosis is absent. Exposure keratitis can occur. Epicanthal folds and hypertelorism are common. Abnormal tearing and aberrant innervation of the lacrimal gland can occur.

Diagnosis

It is a clinical diagnosis.

Clinical conditions that share some clinical features with Möebius syndrome include bilateral palsy of cranial nerve VI, Asymmetrical Crying Facies, brainstem syndromes, Duane syndrome, Kallmann syndrome, myotonic diseases, Poland anomaly, Horizontal gaze palsy with progressive scoliosis (HGPPS) and Klippel-Feil anomaly. In congenital facial palsy, there is isolated loss of the facial nerve nuclei unilateral or bilateral without any other coexistent abnormalities of the brainstem or posterior fossa. Duane syndrome has retraction or retraction equivalents (up shoot and down shoot in adduction), which are not seen in Möebius syndrome. In HGPPS, horizontal gaze palsy occurs associated with scoliosis. The scoliosis is progressive. Patients might have horizontal pendular nystagmus but do not have facial palsy seen in Möebius syndrome. The Imaging findings are very different with a split pons being characteristic of HGPPS. Kallmann syndrome is characterized by anosmia. The presence of vertical eye movement disorders or exotropia should raise consideration of a mutation in *TUBB3* [320]. HOXB1 encodes a transcription factor that is important in rhombencephalon development. Mutations in HOXB1 cause hereditary congenital facial paresis, type 3 (OMIM #614744). These patients do not have bilateral horizontal gaze palsy but have accomodative esotropia [300].

The diagnosis is a clinical diagnosis. There are no specific diagnostic criteria. The presence of congenital bilateral limitation of abduction and facial palsy with the inability to smile is strongly suggestive of Möebius syndrome. Other findings that when present support a diagnostic work-up include

Management

Systemic

"Smile surgery" is being performed which involves muscle transfers, and grafting muscles into the corner of the mouth, in order to facilitate smiles. Though this procedure offers the ability to smile, it does not improve other facial expressions [321].

Ophthalmologic

Some authors report that bilateral medial rectus muscle recession alone may not be adequate and hence advocate a

combination of a medial rectus muscle recession and a lateral rectus muscle resection [322]. In more severe cases muscle transposition has also been reported [322]. The prognosis for vision is good and increasingly better results have been reported with strabismus surgery [322]. Conventional surgical approach for an A-pattern esotropia with bi-medial rectus recession with and appropriate muscle displacement was reported with success [323]. Satisfactory long term surgical results improving parent satisfaction and patient self-esteem have been reported [324]. Lagophthalmos should be managed appropriately with lubricants, antibiotic eye ointment if indicated and exposure keratitis prevented. Tarsorraphy may be required in advanced cases.

Usher Syndrome

Definition

Usher syndrome is a group of autosomal recessive disorders characterized by variable congenital hearing impairment and retinitis pigmentosa with or without vestigular disturbance. A contiguous gene deletion involving the USH1C locus resulting in infantile hyperinsulinism, profound congenital sensorineural deafness, enteropathy, has been reported [325].

There are three major types based on onset and severity of hearing impairment and the presence or absence of vestibular symptoms [326–329] (refer Table 21.6).

Usher syndrome Type I is characterized by congenital profound hearing impairment early retinitis pigmentosa and vestibular dysfunction. *USH1B* accounts for most of the type I Usher syndrome [330].

Usher syndrome Type 2 differs from type I in that the deafness is less severe and slightly later in onset. They have normal vestibular function [331]. *USH2A* gene accounts for 74–90 % of cases of Type 2 Usher syndrome [332].

Usher syndrome Type 3 is characterized by late onset but progressive hearing loss. Patients have mild vestibular dysfunction. Mutations in *CLRN1* (USH3A) are responsible. Onset of retinitis pigmentosa is in late childhood.

Usher syndrome is, in general, a ciliopathy. Photoreceptors, auditory hair cells, and vestibular hair cells develop from ciliated progenitors [333]. A generalized abnormality of axoneme structure is present in patients with Usher syndrome. Most of the mutated genes responsible for Usher syndrome result in loss of hair cells in the inner ear and a gradual and progressive loss of photoreceptors resulting in the phenotype [334]. Mutations in the *MYO7A* gene are the most common cause of Usher syndrome [335].

History

Charles Usher first emphasized the hereditary nature of this condition in 1914 [336].

Epidemiology

Usher syndrome has a worldwide prevalence of 3.5/100,000–6.2/100,000. Usher syndrome was estimated to be responsible for 3–6 % of all childhood deafness and approximately 50 % of all deaf-blindness. The prevalence may be as high as one in 6000 [337]. It is the most common cause of combined

Table 21.6 Usher syndrome: types, genes, proteins and major clincial feature

	Type	Gene	Locus	Proteins	Hearing loss	Vestibular function	Other main findings
Usher 1	A		Does not exist		Congenital profound bilateral	No vestibular response	Early onset of RP
	B	*MYO7A*	11q13.5	Myosin VIIa			
	C	*USH1*	11p15.1	Harmonin			
	D	*CDH23*	10.q22.1	Cadherin 23			Delayed onset of walking
	E						
	F	*PCDH15*	10q21.1	Protocadherin 15			
	G	*USH1G*	17q25.1	Sans			
	H		15q22-q23				
	K		10p11.21-q21.1	–			
	J	*CBI2*	21q21	–			
Usher 2	A	*USH2A*	1q41	Usherin	Mild to severe congenital	Normal vestibular function	No delay in onset of walking
	C	*GPR98*	5q14.3	VLGR1	Higher frequencies		
	D	*DFNB31*	9q32	Whirlin			
Usher 3	A	*CLRN1*	3q25.1	Clarin	Post lingual progressive	Variable vestibular function	Late onset RP
	B	*HARS*	20q	–			

RP Retinitis pigmentosa

deafness and blindness in children and adults in the developed world and second only to congenital rubella in underdeveloped countries. Type I is estimated to occur in at least 4 per 100,000 people. Type 1 Usher syndrome may be more common in certain ethnic populations, Ashkenazi Jews and the Acadian population in Louisiana. Type I appears to be the most common type [338]. Type 3 Usher syndrome is common in the Finnish population. It is the least common form of Usher syndrome.

Systemic Manifestations

Hearing Impairment

The hearing impairment is sensorineural, profound and congenital in Usher Type 1. In Type 2 it is moderate and usually affects the higher frequencies tone. Type 3 has mild but progressive hearing impairment. (Pre-lingual deafness) results in unintelligible speech in Type 1.

Vestibular Disturbance

Vestibular dysfunction differentiates type 1 from type 2 Usher syndrome. All patients with retinitis pigmentosa and hearing loss should be evaluated for vestibular function apart from hearing assessment. People with Usher syndrome type 3 may also experience variable difficulties with balance. As a result of vestibular function, there is a delay in the onset of walking. In Type 2 Usher syndrome, walking starts at normal age. Life span is not affected.

Ophthalmic Manifestations

Retinitis pigmentosa is the main clinical finding. Though there is early onset and progressive visual field loss most patients retain some central vision. Posterior subcapsular cataract can develop early. The overall visual prognosis is poor. Multifocal electroretinography (mfERG) may demonstrate a sharp distinction between the area of reduced function and the central area with remaining normal function [339]. Optical coherence tomography (OCT) may show loss of foveal depression with distortion of the foveal architecture in the macula. Electroretinogram often shows abnormality even in young children with Usher syndrome type 1, even in the absence of fundoscopic signs of retinal degeneration and hence any child with delayed walking and congenital severe deafness should have an ERG [340]. Progressive loss of visual acuity and visual field reaches substansial levels between the second and third decades in both Type 1 and Type 2 Usher syndrome [341]. Usher syndrome shows some important genotype-phenotype correlations. Null MYO7A alleles could be associated with milder dysfunction and fewer photoreceptor structural losses as compared to other genotypes [342].

Diagnosis

The clinical diagnosis can be confirmed by molecular genetic testing. Microarray panel technology is available for clinical use. Smith and coworkers suggested that conditions that can cause retinal dysfunction and congenital deafness like intrauterine infections and perinatal causes should be excluded prior making a diagnosis of Usher syndrome [343]. The differential diagnosis includes congenital rubella syndrome and other congenital infections, deafness dystonia optic neuropathy syndrome (DDON), and other syndromes which have retinal dystrophy with hearing loss such as Alstrom syndrome and Bardet-Beidl. DDON an X linked disorder with optic atrophy occuring in the second decade not consecutive to retinal pathology. Psychiatric symptoms can occur in childhood and dementia invariably occurs by the fourth decade. In some Usher syndrome patients, cataract, mental retardation and psychosis can occur. This is known as Hallgren syndrome [344]. It is important to identify the timing of night blindness as some medications used for psychiatric disturbance can result in a static pigmentary retinopathy (pseudoretinitis pigmentosa). One must also rule out Charles Bonnet syndrome in which hallucinations occur secondary to vision loss. In Hallgren syndrome, the clinical phenotype especially night blindness usually manifests early, before psychiatric symptoms become profound. Vestibular dysfunction results in ataxia.

Management

Systemic

Early cochlear implantation can benefit Usher Type 1 syndrome. Speech discrimination skills, speech production quality, and academic performance have been found to correlate with the age at implant [345].

In the shaker 1 mouse model for Usher type 1B that lacks a functional MYO7A gene, it has been shown that subretinally delivered UshStat, a recombinant EIAV-based lentiviral vector expressing human MYO7A, Expression of GFP and myosin VIIa was documented.

Studies have also shown that subretinally delivered UshStat is safe and well-tolerated in macaque [346, 347]. Adeno associated viral vectors have been used in mice models. Both Lenti viruses and adeno associated virus have been used in animal models with success [348].

Ophthalmic

Consideration of ophthalmic screening for retinitis pigmentosa may be considered for hearing impaired patients. Though early diagnosis of usher syndrome may not assist in improving visual symptoms, early cohlear implantation and intensive speech therapy may immensely benefit the patient in not only improving hearing but also in navigation due to improvement in directional sense.

Waardenburg Syndrome

Definition

Waardenburg syndrome is an autosomal dominant pigmentary disorder with characteristic facial dysmorphism, pigmentary abnormalities of skin, hair and eyes and congenital sensorineural hearing loss. There are four subtypes and multiple subtypes (see Table 21.7). All types except type 2 are characterized by the classical feature of dystopia canthorum (lateral displacement of the medial canthi). Type 3 (Klein-Waardenburg) has limb anomalies and Type 4 (Waardenburg-Shah syndrome) has Hirschsprung disease in addition to other features of Type 1.

Table 21.7 Waardenburg syndrome: diagnostic criteria

Major criteria
Congenital sensorineural hearing loss
White forelock, hair hypopigmentation
Pigmentation abnormality of the iris:
• Complete heterochromia iridium (irides of different color)
• Partial/segmental heterochromia
• Hypoplastic blue irides or brilliant blue irides
Dystopia canthorum, W index >1.95*
Affected first-degree relative
Minor criteria
Skin hypopigmentation (congenital leukoderma)
Synophrys/medial eyebrow flare
Broad/high nasal root, prominent columella
Hypoplastic alae nasi
Premature gray hair (age <30 years)

An individual must have two major criteria or one major and two minor criteria to be considered affected [349]. See Table 21.7 for diagnostic criteria and clinical features.

W index: The measurements required to calculate the W index (in mm) are as follows:

Inner canthal distance (a), interpupillary distance (b), and outer canthal distance (c).

Calculate $W = X + Y + a/b$

$X = (2a - (0.2119c + 3.909))/c$

$Y = (2a - (0.2479b + 3.909))/b$

A W index result >1.95 is considered abnormal.

WS shows extensive phenotypic variability [350]. Mutations in several genes cause Waardenburg syndrome (see Table 21.8). Mutations in *EDN3*, *EDNRB*, *MITF*, *PAX3*, *SNAI2*, and *SOX10* genes causes Waardenburg syndrome Types I and III Waardenburg syndrome are caused by heterozygous mutations in the *PAX3* gene. Type II is caused by mutations in the *MITF* and *SNAI2* genes. Type III is caused by mutations in *SMOC1*. *SOX10*, *EDN3* and *EDNRB* genes also play an important role in the development of nerve cells in the large intestine. Hence mutations in any of these genes results in Type 4 WS. Most of these genes are involved in the formation and development of melanocytes. Apart from contributing to skin, hair, and eye color, melaninplays a critical role in development and functioning of the inner ear where it is found in the stria vascularis. Mutations in any of these genes disrupt the normal development of melanocytes, leading to the clinical phenotype.

History

The classic syndrome was first delineated by Waardenburg in 1951 [351].

Table 21.8 Waardenburg syndrome: types, genes, and clincial features

Type of Waardenburg syndrome	Main feature	OMIM phenotype number	Gene	LOCI
Waardenburg syndrome, Type 1; WS1	Waardenburg syndrome with dystopia canthorum	#193500	*PAX3*	2q35
Waardenburg syndrome, Type 2; WS2A	Waardenburg syndrome without dystopia canthorum	#193510	*MITF*	3p14-p13
Waardenburg syndrome, Type 2; WS2B		600193		1p
WS Type 2C		606662	*WS2C*	8p23
WS2D		608890	*SNAI2*	8q11
WS Type 2E		611584	*SOX10*	22q13
WS2OA	Waardenburg syndrome, Type 2, with ocular albinism	#103470	*MITF* and *TYR*	3p14-p13 and 11q14.3
Waardenburg syndrome, Type 3; WS3 (digenic inheritance)	Waardenburg syndrome withupper LIMB abnormalities	#148820	*PAX3* (AR, AD)	2q36.1
	Klein-Waardenburg			
Waardenburg syndrome, Type 4; WS4A	Waardenburg-shah syndrome with hirschsprung disease	#277580	*EDNRB*	13q22
Waardenburg syndrome, Type 4; WS4B	Waardenburg-shah syndrome	#148820	*EDN3*	20q13
Waardenburg syndrome, Type 4; WS4C			*SOX10*	22q13

Epidemiology

Waardenburg syndrome affects an estimated 1 in 40,000 people. Types I and II are the most common forms and types III and IV are rare. WS Type 4 is less common.

Systemic Manifestations

Dysmorphic Facial Features

Patients have prominent nasal root, round or square tip of nose, hypoplastic alae, smooth philtrum, and a thin upper lip shaped like a cupids bow. Patients may have a wide mandible. The most important feature, dystopia canthorum, or lateral displacement of the medial canthi, which is defined by the W index as detailed below. WS type 2 can be differentiated from Type 1 in that there is normal canthal index in type 2.

Hearing Loss

Hearing impairment is one of the most consistent non-ocular findings in Waardenburg Syndrome. The deficit is sensorineural, congenital and typically non-progressive. It can be unilateral, bilateral or asymmetric. There is significant intrafamilial variation in the severity and laterality of the hearing loss. The temporal bone shows several abnormalities including enlargement of the vestibular aqueduct and upper vestibule and narrowing of the internal auditory canal opening, absence of cochlear nerve, bilateral agenesis or hypoplasia of the semicircular canals or both, associated with a cochlear deformity [352].

Hair Color

Hair can show several pigmentary abnormalities, the most common being the presence of a frontal white forelock of hair. The white forelock may be present at birth and may disappear or become more evident in the second decade. A history of using hair dye needs to be elicited in a patient who is suspected to have Waardenburg syndrome but does not have the white forelock. It is usually in or near the midline but occasionally may be seen in other areas. There may be a family history of premature graying of scalp hair without the white forelock [353]. Rarely, a black forelock can occur [354].

Limb Anomalies

The association of limb anomalies with Waardenburg syndrome was first reported by Kline [355]. Upper limb anomalies include hypoplasia of the musculoskeletal system, flexion contractures, fusion of the carpal bones, syndactyly, and flexion contractures of the fingers [356]. A child with dystopia canthorum, partial albinism, and very severe upper-limb defects was reported and the child was born to parents who both had mild Type I, was found to be homozygous for *PAX3* (Type 3) [357].

Hirsprung Disease

Hirschsprung disease (aganglionic megacolon; 142623) was first observed in patients with Waardenburg syndrome by McKusick [358]. Subsequently this association was observed by many [358, 359]. A defect in the neural crest was suggested as a possible cause in a child with bicoloured iris and Hirschsprung disease [360]. It is seen in Waardenburg syndrome type 4 and is caused by heterozygous mutations in *EDNRB* gene. Dystopia canthorum may or may not be present.

The mutation was found to be dose sensitive with both heterozygotes and homozygoted having risk for developing Hirschsprung disease [361].

Other Findings

Other less common findings that have been reported include cleft lip, [362] cleftpalate or spina bifida [363] and leukoderma. An unusual demyelinating peripheral neuropathy has been reported in a patient [364].

WS type 2 can be differentiated from Type 1 in that there is normal canthal index in type 2. Hearing impairment, heterochromia iridum are more common in Type 2 while white forelock and leukoderma are more common in Type 1.

Ophthalmic Manifestations

It is characterized by bushy eyebrows with medial eyebrow flare or, occasionally synophrys. The most consistent feature is dystopia canthorum [365]. Hypertelorism is seen in all subtypes except type 2. Pigmentary abnormalities of the eye include heterochromia irides, and pigmentary abnormalities of the fundus in the form of retinal pigment epithelial mottling. The heterochromia can be complete or segmental. Hypoplasia of the iris and brilliant blue irides can occur. Iris and choroidal hypopigmentation have been reported. Eyebrows and eyelashes may be also show hypopigmentation in some patients. Medial eye brow flare is more common and consistent than synophrys.

Diagnosis

Diagnosis of Waardenberg syndrome is based on diagnostic criteria (Table 21.1).

The differential diagnosis includes piebaldism (172800), an autosomal dominant disorder which can sometimes coexist with Waardenburg syndrome (see Fig. 21.7a, b). The ocular findings of dystopia canthorum and pigmentary abnormalities of the eye are very rare in isolated piebaldism. Piebaldism is characterized by ventral amelanotic patches on

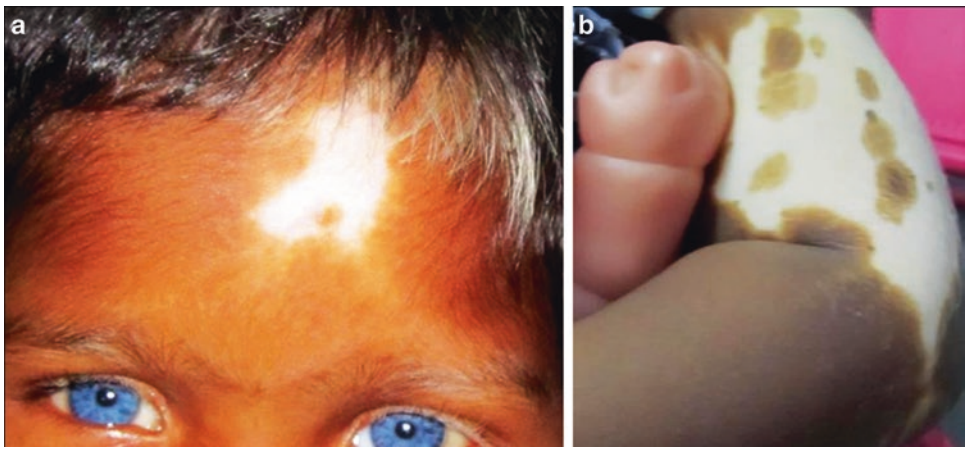

Fig. 21.7 Waardenburg syndrome with Piebaldism. (**a**) Photograph of a female child with piebaldism and Waardenburg syndrome. (**b**) Skin findings in the same patient due to piebaldism (Photo courtesy Dr. P. Vijayalakshmi, Aravind Eye Care System, Madurai)

the skin, sometimes with hyperpigmented borders [366]. Mutations of the genes *KIT* and *SNAI2* are responsible for piebaldism. Tietz syndrome (OMIM 277740) is characterised by white forelock of hair and multiple malformations [356]. Other findings in this syndrome include atrial septal defect, prominent thoracic and abdominal veins, hypoplastic or absent terminal phalanges of toes. Segmental atelectasis of the lungs due to segmental bronchomalacia was also observed. X linked carriers of Ocular albinism may manifest abnormal iris. A overlap of ocular albinism and Waardenburg syndrome has also been reported [367]. A digenic pattern of inheritance with mutations involving the *MITF* and *TYR* genes was suggested [368].

Management Recommendations

Ocular

Prognosis is excellent and no ophthalmic problems require specific management.

Systemic

Cochlear implant has been shown to be successful [369].

Weill-Marchesani Syndrome

Definition

Weill-Marchesani Syndrome (WMS) is a rare disorder primarily affecting connective tissue and the eyes. Alternative names that were used earlier include spherophakia-brachymorphia syndrome and congenital mesodermal dysmorphodystrophy. It is characterized by lens abnormalities, proportionate short stature, brachydactyly and joint stiffness [370]. Autosomal recessive inheritance is more common than autosomal dominant. A WMS-like syndrome sharing some features of WMS like ectopia lentis, microspherophakia and cardiac defects has been reported. However brachydactyly and joint stiffness are absent [371].

The autosomal recessive form is due to homozygous mutations in *ADAMTS10* gene [372]. Mutations in *LTBP2* have also been shown to cause autosomal recessive WMS [373]. The autosomal dominant form occurs due to mutations in the gene *FBN1*, the gene that makes fibrillin [374]. They usually have an affected parent and mutations in which are also responsible for Marfan syndrome. ADAMTS10 is a member of the extracellular matrix protease family and is expressed in skin, fetal chondrocytes, and fetal and adult hearts. This protein plays a role in development of the eyes, heart, and skeleton. Interaction between *ADAMTS10* protein and FBN1 protein has been demonstrated [375].

History

Weill first described the features in 1932 followed by Marchesani in 1939 [376, 377].

Epidemiology

The estimated prevalence of WMS is 1 in 100,000 people.

Systemic Manifestations

Skeletal

Proportionate short stature is the most consistent clinical finding. Patients also exhibit brachydactyly due to shortening to the metacarpals. They may experience poor mobility

of the joints that can give the hands a somewhat clenched appearance and leaves the elbows incompletely extended. Primary osteoporosis has also been reported [378]. Joint limitations appears to more common in autosomal dominant WMS [379].

Cardiac

Reported cardiac abnormalities include aortic stenosis, prolonged QT interval, and mitral valve pathology [380]. If there are no cardiac abnormalities the prognosis for life is good. Cardiac anomalies appears to more common in autosomal recessive WMS [379].

Dental Anomalies

Other

Intelligence is usually normal but mild intellectual disability can occur [379].

Ophthalmic Manifestations

The primary lenticular abnormality is microspherophakia, which usually remains central although subluxation can occur. Patients have lenticular myopia. The lens position becomes progressively anterior resulting in angle closure as the iris is pushed forward. Lens contact with the iris also may cause posterior synechia and iris atrophy which is often paradoxically worse on the anterior surface of the iris. Secondary glaucoma results from angle closure. Rarely, corneal decompensation can occur due to intermittent lenticular-endothelial touch. Blunt ocular injury can predispose to dislocation of the lens due to trauma induced weakening of the zonules Patients with autosomal dominant WMS have a lower incidence of lens related problems. Liquefied vitreous has been reported in the autosomal dominant form of WMS [381]. The central corneal thickness has been found to be higher [382] and can cause falsely high IOP measurements and might make management of glaucoma difficult.

Diagnosis

There are no specific diagnostic criteria. There are several conditions that cause ectopia lentis but most of them (Marfan, homocystinuria, sulfite oxidase deficiency) cause tall stature with or without arachnodactyly in contrast to short stature and the brachydactyly seen in WMS. Ectopia lentis et pupillae is an autosomal recessive disorder characterized by correctopia (displacement of the pupil) and the lens in the opposite direction. These patients are systemically normal and have anormal sized lens without progressive anterior migration. Although they do have persistent pupillary membrane strands to the lens surface, best seen after pupil dilation, these arise form the iris collarette rather than the pupil margin as in posterior synechia. Glaucoma-lens ectopia-microspherophakia-stiffness-shortness (GEMSS) syndrome closely resembles WMS [383]. A WMS like syndrome sharing all other clinical features except brachydactyly and joint stiffness has also been described [371]. Mutations in ADAMTS17 has been reported to cause WMS like syndrome [371].

Management: Recommendations

Systemic Management

Maxillary hypoplasia, misalignment of teeth and neck stiffness can cause difficulty in intubation for anesthesia [384]. Preoperative cardiac assessment and echocardiography are recommended. Intra venous induction and a reinforced laryngeal mask airway (RLMA) has been recommended to avoid the difficulties with endotracheal intubation and a cardio-stable anesthesia is recommended [385].

Ophthalmic

The lenticular myopia is often high and cannot be satisfactorily corrected by glasses. Further the refraction is often fluctuating and contributes to amblyopia. Miotics are contraindicated as they can precipitate further anterior lens movement with acute angle closure. In young children, strong cycloplegic agents, such as topical atropine, may initially have some success in deepening the anterior chamber by posterior rotation of the iris-ciliary body diaphragm. Peripheral iridectomy is rarely helpful. Rather, early lensectomy, before the angle begins to close, may prevent the development of glaucoma. Lensectomy is also technically much more challenging later as the anterior chamber can be narrowed to a slit over time. Patients are best left aphakic as an intraocular lense implant in the bag will also be susceptible to anterior movement. In addition, the capsular bag in these children is often found to be quite abnormal, lacking the normal tensile strength of an unaffected lens, sometimes crinkling up into a lens membrane made after the lens is removed.

If glaucoma develops and is not manageable by medications, surgical planning must keep in mind the peripheral irido-corneal adhesions that invariably develop, especially if the lens is not removed early. This may make tube placement challenging. Intraocular pressure measurement must be considered in view of increased CCT if present.

Table 21.9 provides a comprehensive, but incomplete, list of syndromes of ophthalmic importance.

Table 21.9 Genes, loci, ophthalmic and systemic features of some syndromes of ophthalmic importance

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Acro-Dermato-Ungual-Lacrimal-Tooth (ADULT) It is an allelic disorder of Hay-Wells syndrome/ulnar mammillary syndrome	103285	*TP63*	3q28	AD	Lacrimal duct atresia nasolacrimal duct obstruction	Ectrodactyly,
						syndactyly,
						Finger and toenail dysplasia,
						Hypoplastic breasts and nipples,
						Intensive freckling,
						Primary hypodontia
						Photosensitive skin sparse hair
						Frontal alopecia
Ankyloblepharon-Ectodermal defects-Cleft lip/palate (AEC) syndrome (Hay-Wells)	106260	*TP63*	3q28	AD	Ankyloblepharon filiforme adnatum	Cleft Lip
					Lacrimal punctal atresia	Cleft Palate
						Syndactyly
						Camptodactyly
						Ectrodactyly
						Hearing loss
						Hypospadias
Arts	301835	*PRPS1*	Xq22.3	XLR	Optic atrophy and Nystagmus	Intellectual disability
Charcot-Marie-Tooth type 5 (cmtx5)						Profound congenital sensorineural hearing impairment
Fatal X-linked mental retardation-- ataxia-deafness						Early-onset hypotonia and delayed motor development, Ataxia, seizures, Areflexia
						Recurrent upper respiratory tract infections
Athabascan syndrome (ABDS) and Bosley-Salih-Alorainy syndrome (BSAS)	601536 601853	*HOXA1*	7p15.2	AR	Congenital horizontal gaze palsy	Developmental delay
						Seizures
						Deafness
						Central hypoventilation
						Vestibular abnormalities
						Congenital cardiac defects
						Vocal cord weakness/paralysis
						Internal carotid abnormalities
Branchio-oculo facial	113620	*TFAP2A*	6p24.3	AD	Strabismus	Bronchial cleft sinuses
					Nasolacrimal duct obstruction	Broad nasal bridge protruding upper lip
						Carp-shaped mouth
CAPOS syndrome	601338	*ATP1A3*	19q13.3	AD	Optic atrophy	**C**erebellar ataxia,
						Areflexia
						Pes cavus
						Sensorineural hearing loss

CCFDN—Congenital cataracts, Facial dysmorphism, and Neuropathy	604168	*CTDP1*	18q23	AR	Bilateral congenital cataracts, microcornea, microphthalmia,	Demyelinating, symmetric, distal peripheral neuropathy
					Miosis	Developmental delays and intellectual deficit
					Mildly dysmorphic facial features	Short stature
					Nystagmus	Hypo gonadotropic hypogonadism
						Para infectious rhabdomyolysis is a potentially life-threatening complication can occur following infections.
Chanarin-Dorfman	275630	*CGI58 gene*	3p21.33	AR	Cataract	Congenital ichthyosis
Neutral lipid storage disease with ichthyosis					Nystagmus	Hepatosplenomegaly,
						Vacuolated granulocytes (Jordans anomaly), myopathy
Chitayat-Hall	208080	*Not yet identified*	*Not yet identified*	AR	Facial anomalies ('boxy' head, square face, small tipped nose, Chubby cheeks, and micrognathia microcephaly. oval face with frontal bossing, full cheeks, small nose with depressed nasal bridge, microphthalmia, retinal coloboma.	Distal Arthrogryposis (Camptodactyly of fingers and hammertoes), hypopituitarism, severe mental retardation,).
						Aminoaciduria, hypokalemia,
						Abnormal/incomplete thoracic vertebrae.
						Delayed myelination in neuroimaging
						Reduction in cortical folding
Cleidocranial dysostosis (CLCD)	119600	*RUNX2*	6p21.1	AD	Hypertelorism	Persistently open skull sutures
						Bulging calvaria, hypoplasia or aplasia of the clavicles, wide pubic symphysis, short middle phalanx of the fifth fingers, dental anomalies
						Vertebral malformations
						Wermian bones
						Syringomyelia
						Scoliosis
Coffin-Siris	135900	*ARID1A, ARID1B, SMARCA4, SMARCB1, or SMARCE1 gene*	7q32.34	AR	Ptosis	Thick eyebrows, flat nasal bridge, anteverted and wide nasal tip
						Intellectual disability coarse facial features
						Hypertrichosis
						Hypoplastic or absent fifth fingernails or toenails
						Generalized hypertrichosis, scalp hypotrichosis, absence of the distal phalanges of the fifth fingers and of the second to fifth toes, small patellas, inguinal hernia
						Sucking and feeding difficulties.
						Dandy-Walker malformation
						Endocrinologic deficiency

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
COFS	MIM 214150	*ERCC6 gene*	10q11	AR	Congenital cataracts	Facial dysmorphism
There are four subtypes COFS-1 is referred as Pena-Shoker					Microphthalmia	Prominent nose, micrognathia
					Nystagmus	Large ear pinna overhanging upper lip.
						Congenital microcephaly,
						Severe mental retardation
						Severe developmental delay
						Post natal growth failure
						Arthrogryposis
						Hypotonia
						Failure to thrive
						Widely set nipples
						Kyphoscoliosis
						Osteoporosis
						Hearing loss
						Seizures
						Hypoplasia of the corpus callosum, ventriculomegaly
						Delayed myelination
						Intra cranial calcification
						Cryptorchidism
Cohen syndrome	MIM 216550	*VPS13B*	8q22.2	AR	High myopia	Facial Dysmorphism:
					Retinal dystrophy	Microcephaly (usually mild)
						Thick hair,
						Thick eye brows and lashes and low hairline
						Wide and wave-shaped palpebral fissures.
						Short philtrum, apparently prominent central incisors and a
						Grimacing on attempted smiling.
						High nasal bridge, maxillary malar hypoplasia, and upslanting
						Long and tapering fingers
						Hyper extensibility of the joints
						Truncal obesity
						Intellectual disability
						Cerebellar hypoplasia/degeneration
						Prominent Corpus callosum
						Intermittent isolated neutropenia,
						Cheerful disposition and psychomotor retardation
						Childhood hypotonia
						Isolated growth hormone deficiency
						Increased space between the first and second toes (sandal gap)
						Repeated gingival or skin infections
						A relatively enlarged corpus callosum in a microcephalic head associated with normal gray and white matter signal intensity should alert the clinician to suspect Cohen syndrome.
						Laryngomalacia, laryngeal stenosis, and vocal cord paralysis

Cerebro-Oculo-Nasal Syndrome	605627	*Not yet known*	Not yet known	AD	Ocular hypertelorism, Telecanthus, Epicanthic folds, downslanting palpebral fissures, medial abnormally placed eyebrows, and sparse eyelashes	Malar hypoplasia, a large philtrum, a High-arched and narrow palate, posteriorly rotated ears
						Hypoplastic tragus
						A proboscis-like appearance of the nose presence of small and atypical appendage-like structures.
					Anophthalmia	Developmental delay.
Ectrodactyly, ectodermal dysplasia, and cleft lip/palate (EEC1)	129900	*Not yet known*	7q11.2-q21.3	AD	Keratitis	Ectrodactyly
					Photophobia, blepharitis,	Cleft lip
					Entropion,	Cleft palate
						Growth hormone deficiency
						Anomalies of the urinary tract
						Genital anomalies
						Choanal atresia
						Hearing loss (sensory and conductive)
Facio-Oculo-Acoustic-Renal (FOAR) syndrome)/Donnai Barrow syndrome (DBS)	222448	*LRP2*	2q31.1	AR	Hypertelorism, down-slanting	Moderate sensorineural hearing loss
					Palpebral fissures, macrocephaly, broad forehead, and an enlarged anterior fontanelle, facial anomalies	Low molecular weight
					Iris coloboma, iris hypoplasia	Proteinuria
					Cataract, High myopia, retinal detachment, posterior subcapsular lens opacity, choroidal atrophy	Hypertelorism and either CDH or omphalocele by prenatal imaging should raise suspicion of DBS.
Fasio scapulohumeral dystrophy (FHSD)	158900		4q35	FHSD1 is AD	Lagophthalmos	Muscular weakness especially involving the face, shoulder and upper limb
			SMCHD1 and D4Z4	FSHD2 is digenic	Exposure keratitis	Winging of the scapula
					Peripheral retinal nonperfusion with secondary terminal neovascularization, exudate and hemorrhage	Foot drop
						Hearing loss
						Rarely cardiac abnormalities
Frank-Terhaar syndrome; FTHS/	249420	*TKS4*	5q35.1	AR	Prominent forehead, hypertelorism, downslanting palpebral fissures, broad and flat nasal bridge, broad nasal tip, anteverted nostrils, high-arched palate, gingival hypertrophy	Short stature
Melnick-Needles		*SH3PXD2B*			Megalocornea	Mental retardation
					Congenital glaucoma	Multiple skeletal abnormalities
					Hypertelorism	Developmental delay
						Large anterior fontanel, pectus excavatum, prominent coccyx

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Fraser	MIM 219000	*FRAS1, FREM2*	4q21.21	AR	Cryptophthalmia	Facial Dysmorphism:
		GRIP1	12q14.3		Microphthalmia	Cryptophthalmos (most common abnormality)
			13q13.3		Nasolacrimal duct malformation/obstruction	Microphthalmia, anophthalmia
						Hypertelorism
						High palate
						Cleft lip/cleft palate
						Laryngeal stenosis
						Fusion of labia and enlargement of clitoris,
						Bicornuate uterus and malformed fallopian tubes
						Cryptorchidism in males
						Ambiguous genitalia
						Renal agenesis (unilateral or bilateral)
						Syndactyly
						Middle and outer ear malformations.
Growth retardation-Alopecia-Pseudoanodontia-Optic atrophy (GAPO)	230740	*ANTXR1*	2p13.3	AR	Frontal bossing, high forehead, mid-facial hypoplasia and wide-open anterior fontanel, depressed nasal bridge, Large ears, prominent cheeks, thin lips, large tongue, unerupted teeth, micrognathia	Short stature
					Optic atrophy	Progeria like appearance
						Alopecia
						Dilated cardiomyopathy
						Large genitalia.
Gillespie	206700	*PAX6*	11p13	AR	Aniridia	Cerebellar ataxia
						Intellectual disability
						Developmental delay
						Speech delay
Gomez-Lopez- Hernandez (GLH)	601853	*Not yet known*	Not yet known	Not yet known	Hypertelorism	Triad of rhombencephalosynapsis, trigeminal anesthesia, often giving rise to corneal opacities, and bilateral parietal or parietooccipital alopecia
Cerebello-Trigeminal-Dermal dysplasia					Corneal opacities secondary to corneal hypoesthesia	Craniosynostosis
					Ptosis	Mid-face hypoplasia, scalp alopecia, low-set and posteriorly rotated ears,
					Strabismus	Common:
						Rhombencephalosynapsis (fusion of cerebellar hemispheres, agenesis or hypogenesis of the vermis, fusion of the dentate nuclei and the superior cerebellar peduncles)
						Ataxia, trigeminal anesthesia, cerebellar anomalies
						Mental retardation, short stature and partial growth hormone deficiency
						Psychiatric disorders
						Absence of the septum pellucidum, ventricular enlargement with a thin cortex are other findings

Hallerman- Streiff-Francois	234100			New dominant mutation/AR	Microphthalmia	Facial Dysmorphism
	257850	*GJA1*	6q22.31	AR	Cataract (can be self-absorbing)	hypotrichosis, microphthalmia, cataracts, 'Bird-like' face
					Strabismus	Beaked nose, micrognathia, skin atrophy, dental anomalies, and proportionate short stature.
					Nystagmus	Lack of mandibular angle and hypoplasia of the clavicles and ribs.
						Snoring and/or daytime hypersomnolence
						Tracheomalacia
Heimler	234580	*PEX1*	7q21.2	AR	Retinal dystrophy	Sensorineural hearing loss
		PEX6	6p21.1			Beau lines on nails
						Leukonychia
						Tooth enamel hypoplasia
						Amelogenesis imperfecta
HGPPS—Horizontal gaze palsy with progressive scoliosis	607313	*ROBO3*	11q24.2	AR	Congenital horizontal gaze palsy	Progressive scoliosis
						Butterfly shaped medulla with anterior flattening and an unusual midline cleft.
						Flattening of the basis pontis and hypoplasia of the pontine tegmentum
						Absent or hypoplastic abducent nerve nuclei, the medial longitudinal fasciculus, and the pontine paramedian reticular formation are also involved
						There is no other significant neurological abnormality.
Jalilli Cone-rod dystrophy and Amelogenesis Imperfecta	217080	*CNNM4*	2q11.2	AR	Cone rod dystrophy	Amelogenesis imperfecta
					Photophobia	Dental caries
					Nystagmus	
Jeune syndrome Short-rib thoracic dysplasia SRTD1	208500	*ATD*	15q13	AR	Retinal degeneration resembling Leber congenital amaurosis	Long, narrow thorax, short stature, short limbs, polydactyly, Renal cystic disease, skeletal findings like cone-shaped epiphyses in hands and feet, irregular metaphyses, shortened ilium, and trident-shaped acetabulum
						Hepatic fibrosis
SRTD-2	611623	*IFT80*	3q25.3			Congenital hydrocephalus
SRTD-3	613091	*DYNC2H1*	11q22.3			'Trident' appearance of the acetabular roof
SRTD-4	613819	*TTC21B*	2q24.3			
SRTD-5	614376	*WDR19*	4p14	AR		
SRTD-6	263520	*NEK1*	4q33			
SRTD-7	614091	*WDR35*	2p24.1			
SRTD-8	615503	*WDR60*	7q36.3			
SRTD-9	266920	*IFT140*	16p13.3			
SRTD-10	615630	*IFT172*	2p33.3			
SRTD-11	615633	*WDR34*	9q34.11			
SRTD-13	616300	*CEP120*	5q23.2			
SRTD-14	616546	*KIAA0586*	14q23.1			

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Johanson-Blizzard syndrome	OMIM 243800	*UBR1 gene.*		AR	Upslanting palpebral fissures	Facial Dysmorphism:
					Nasolacrimal duct malformations	Aplasia or hypoplasia of the nasal alae, small beaked nose, abnormal hair patterns or scalp defects, and oligodontia
						Mental retardation usually mild
						Hypothyroidism, pancreatic exocrine insufficiency
						Sensorineural hearing loss,
						Imperforate anus
						Urogenital abnormalities, polycystic dysplasia of the kidneys and hydro ureter, double vagina and double uterus.
						ASD, dilated cardiomyopathy
						Total situs inversus
Kabuki syndrome	OMIM 147920	*KMT2D*	12q13.12	AD	Arched eyebrows, long eyelashes, Long palpebral fissures with partial eversion of lateral lid margin of lower eye lid (euryblepharon)	Developmental delay and intellectual disability
		KDM6A		X LD	Ptosis, epicanthic folds, strabismus, blue sclera, nystagmus	Short stature
						Microcephaly
						Seizures, hypotonia
						Cleft palate
						Persistent fetal finger pads, clinodactyly, brachydactyly
						Otitis media and hearing loss
						Large protuberant ears
Klippel-Feil anomaly	118100	*GDF6*	8q22.1	AD	Möebius syndrome, Duane syndrome (Wildervanck syndrome)	Hearing loss (sensorineural, conductive, or mixed type), Scoliosis, Sprengel anomaly and facial asymmetry
Klippel-Feil syndrome (KFS1)						Malformation of laryngeal cartilages
						Fusion of the carpal and tarsal bones, and restricted flexibility of the hands, wrists, elbows, feet, and legs
						External ear malformation, ossicular chain abnormalities, and structural abnormalities of the inner ear
						Cleft palate
KFS2	214300	*MEOX1*	17q21.31	AR		
KFS3	613702	*GDF3*	12p13.31	AD		
KFS4	616549	*MYO18B*	22q12.1	AR		Myopathy facial dysmorphism

Kniest Dysplasia	156550	*COL2A1*	12q13.11	AD	Myopia	Short stature (disproportionate with short chest)
					Retinal detachment	Widening of the joints
					Glaucoma	Pain and stiffness with restriction of joint movements
					Cataract	Dumb bell shaped long bones, Club foot
					Ectopia lentis	Kyphoscoliosis
						Hearing impairment
						Inguinal and umbilical hernia
						Tracheomalacia
						Cleft palate
Knobloch	267750	*COL18A1*	21q22.3	AR	Pathological myopia	Occipital alopecia, cutis aplasia, bony abnormality or encephalocele
					Geographic macular atrophy	
					Retinal detachment	
					Vitreoretinal degeneration	
					ectopia lentis	
					Cataracts	
					Featureless iris	
Lacrimo-Auriculo-Dento-Digital (LADD)	149730	*FGFR2*	10q26.13	AD	Nasolacrimal duct obstruction	Hearing abnormalities usually mixed hearing loss
Levy-Hollister		*FGFR3*	4916.3		Aplasia of the punctum	Cupped ears
		FGF10	5p12		Alacrima	Dental anomalies including Hypodontia
						Limb anomalies
						Pre-axial polydactyly
						Digitalization of the thumb
						Renal agenesis
Lathosterolosis	607330	*SC5DL*	11q23.3	AR	Cataract	Microcephaly, receding forehead, anteverted nares, micrognathia, prominent upper lip, highly arched palate,
Sterol C5-Desaturase Deficiency						Multiple congenital anomalies, intellectual disability, postaxial hexadactyly, syndactyly
						Arnold-Chiari malformation
						Increased levels of lathosterol in cells and plasma
Lenz microphthalmia	300166	*BCOR*	Xq11.4	X LR	Colobomatous or non-colobomatous microphthalmia	Microcephaly
Oculo-Facial-Cardio-Dental					Ptosis	Cleft lip, cleft palate and abnormal spacing of teeth.
					Cataract	Thumb duplication or hypoplasia
						Syndactyly, camptodactyly, clinodactyly,
						Hypospadias, cryptorchidism and urogenital anomalies
						Narrow thorax and sloping shoulders
						Renal agenesis, hydronephrosis
						Cardiac abnormality
						Cognitive impairment

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Limb-Mammary Syndrome (LMS)	603543	*TP63*	3q28	AD	Nasolacrimal duct obstruction	Hypohidrosis,
						Hypodontia
						Cleft palate
						Hypergonadotropic hypogonadism
LOGIC	245660	LAMA3	18q11.2	AR	Conjunctival scarring	Altered cry
laryngeal and ocular granulation tissue in children from the Indian subcontinent						Defective enamel of teeth
						Granulation formation and subsequent ulceration
						Usually fatal
Macroblepharon, Ectropion, Hypertelorism, and Macrostomia (MEHM)	602562	*Not yet found*	Not yet found	Not yet determined	**Ocular**:	**Dysmorphic facial features:**
Verloes-Lesenfants					Lagophthalmos	Severe hypertelorism, large palpebral fissures, lower lid ectropion, broad raised nasal base, a wide nasal tip, long smooth philtrum, macrostomia, irregularly placed teeth and Micrognathia.
					Corneal xerosis, secondary Chronic conjunctivitis and exposure keratitis.	Mandibulo-facial dysostosis
						Large fontanels, broad metopic suture, and osseous hypertelorism
Marden-Walker	248700	*PIEZO2*	18p11.22-p11.21	AD	Blepharophimosis	Micrognathia, kyphoscoliosis,
MWKS						Limb contractures, pigeon breast, arachnodactyly
						Renal microcystic disease
						Joint contracture
Marinesco-Sjogren Syndrome (MSS)	248800	*SIL1*	5q31.2	AR	Congenital cataracts	Cerebellar ataxia,
						Progressive myopathy
						Delayed psychomotor development
						Short stature
						Hyper-gonadotropic hypogonadism,
						Skeletal deformities
						Increased serum creatine kinase
						Muscle biopsy shows chronic dystrophic changes
Martsolf	212720	*RAB3 GAP2*	1q41	AR	Congenital cataract	Intellectual disability
Cataract-Mental Retardation-Hypogonadism					Microphthalmia	Hypogonadism
					Microcornea	Short stature
						Digital anomalies
						Micropenis
						Cryptorchidism
Matthew-Wood	601186	*STRA6*	15q24.1	AR	Microphthalmia/hypoplastic or absent optic nerves	Diaphragmatic defect
						Neonatal respiratory distress
					Cystic eye	Hypoplastic and often malformed lungs
						Congenital Cardiac malformations
						Diaphragmatic hernia
						Hiatal hernia
						Renal abnormality

Micro syndrome	600118	*RAB3GAP1*	2q21.3	AR	Microcephaly	Cortical dysplasia,
Warburg micro syndrome-1 (WARBM1)					Microspherophakia	Pachygyria
					Prominent root of the nose, large anteverted ears, facial hypertrichosis	Hypoplasia of the corpus callosum, severe mental retardation, spastic diplegia, hypogonadism
					Microphthalmia, microcornea, membranous cataracts, optic atrophy,	Hypotonia, mild to moderate spastic palsy with hip dislocations
					Miosis	Developmental delay
					Posterior synechiae	Urinary incontinence
						Ectopic kidney
						Bulbous nose
Mohr-Tranebjaerg	304700	*TIMM8A*	Xq22.1	X LR	Progressive visual loss due to optic atrophy	Progressive sensory neural hearing loss (pre lingual or post lingual
Deafness-Dystonia-Optic Neuropathy (DDON)					Photophobia	Normal vestibular function
					Reduced visual acuity,	Dystonia (Not seen in MELAS)/Ataxia
					Acquired color vision defect, and central scotoma.	Brisk tendon reflexes (unlike as in Friedreich ataxia), ankle clonus, and extensor plantar responses
					Retinal evaluation and ERG is normal	Behavioral problems
						Dementia
						Dysphagia and aspiration pneumonia
						Normal fertility
						No Cardiomyopathy (Common in Friedreich ataxia, which is an autosomal recessive disorder)
						Muscle biopsy shows normal mitochondria, normal enzyme activity.
						No Anorexia and recurrent vomiting as in MELAS
						Agammaglobulinemia as part of the contiguous gene deletion syndrome when the *BTK* gene is also involved.
MORM	610156	*INPP5E*	9q34.3	AR	Non-progressive visual impairment	Small penis in the absence of testicular abnormalities (Different from BBS)
Mental retardation					Mottled retina	Polydactyly
Obesity						
Retinal dystrophy						
Micropenis						
Mowat-Wilson syndrome	235730	*ZEB2*	2q22.3	AD	Microphthalmia	
					Cataract	
					Coloboma	
					Posterior embryotoxon	

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Nail Patella syndrome (NPS)	161200	*LMX1B*	9q33.3	AD	Juvenile open angle glaucoma (JOAG), ptosis, microcornea, microspherophakia, cataract, keratoconus	Nail hypoplasia, splitting of the nails, longitudinal ridging of nails
					Listers sign (dark central pigmentation usually petaloid shaped iris	Hypoplastic patella, absent patella, hypoplastic lateral femoral condyle
						Proteinuria, hematuria, renal failure, palpable iliac spur in mid-part of the ilium
						Psychosis, limitation of joint motility (supination and pronation of forearm, knees, renal failure), hypoplastic scapulae
Nance-Horan syndrome (NHS)	302350	*NHS*	X p22.13	X LR	Congenital cataract	Dysmorphism
					Microcornea	Large pointed anteverted ears
						High nasal bridge
						Dental anomalies
						Supernumerary centrally situated upper incisor
						Hutchinsonian incisors
						Developmental delay
						Intellectual disability
Neuhauser	249310				Megalocornea	Frontal bossing, hypertelorism, depressed and broad nasal root, long philtrum, micrognathia, and high-arched palate.
Megalocornea-mental retardation						Bifid uvula
						Cerebral cortical atrophy
Nicolaides-Baraitser syndrome (NBS)	601358	*SMARCA2*	9p24.3	AD	Vitreoretinopathy	Dysmorphic features:
					Glaucoma	Brachycephaly, thick
						Medially sparse eyebrows
						Long lashes
						Deep-set eyes
						Severe Mental retardation
						Sparse scalp hair with normal eyebrows and
						Eyelashes
						Flaredalaenasi, low columella, broad and long philtrum, ears with thick overfolded helices, wide mouth, and large protruding tongue, thick and everted lower vermilion, and frequent drooling
						Prominent lower lip, brachydactyly, and prominent interphalangeal joints.
						Refractory seizures, Short stature, obesity, complete alopecia, eczema,
						Narrow nasal bridge, broad nasal base and tip,

Nikawa-Kuroki Kabuk2	300867	*KDM6A*	Xp11.3	XLD	Long eyelashes, long palpebral fissures with eversion of the lateral third of the lower eyelids (similar to the make-up of actors of Kabuki, a Japanese traditional theatrical form)	Peculiar facies, a broad and depressed nasal tip, prominent and large earlobes, a cleft palate
					Strabismus	Postnatal dwarfism,
						Scoliosis, short fifth finger,
						Persistence of foetal finger pads,
						Recurrent otitis media in infancy
						Radiographic abnormalities of the vertebrae, hands, and hip joints
						Hirsuitism
Noonan	163950	*PTPN11, SOS1,, RAF1, KRAS, RAS, BRAF, MAP2K1*		AR	Blue or blue-green iris, hypertelorism,	Short stature and developmental delay
					Epicanthal folds thick lids or ptosis	Congenital heart defect
					Strabismus, refractive errors, amblyopia, and nystagmus	Webbed neck
						Apparently low-set nipples
						Cryptorchidism
						Pulmonary valve stenosis
						Hypertrophic cardiomyopathy
						Structural defects frequently observed include atrial and ventricular septal defects, branch pulmonary artery stenosis
						Bleeding diathesis/coagulopathy/bruising
						Lymphedema
						Genitourinary abnormalities
						Increased risk for
						Arnold-Chiari I malformation
						Hepatosplenomegaly
						Juvenile myelomonocytic leukemia (JMML)
						Low-set, posteriorly rotated ears with fleshy helices
						Can be associated with NF1
Oculoauricular	612109	*HMX1*	4p16.1	AR	Microphthalmia, microcornea, anterior segment dysgenesis, cataract, ocular coloboma, retinal pigment epithelium abnormalities, rod-cone dystrophy,	External ear malformations

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Oculo-Dento Digital Dysplasia (ODDD)	257850	*GJA1*	6q22.31	AD	Prominent epicanthic folds	Narrow, pinched nose with hypoplastic alaenasi, prominent columella and thin anteverted nares together with a narrow nasal bridge
				AR	Microphthalmia, microcornea	Microdontia
					Glaucoma, optic nerve dysplasia	Dental caries
					Retinal dysplasia	Syndactyly
						Camptodactyly
						Spastic paresis
						Abnormal white matter changes in brain
						Sparse scalp hair
						Nail abnormalities
						Lymphedema
Oculoectodermal	600268	*Not Yet Known*	Not Yet Known	Possible new mutation	Epibulbar Dermoids	Aplasia cutis congenita
				Possible AR cannot be excluded	Strabismus	Cutaneous hyperpigmentation
					Eyelid coloboma	Macrocephaly
						Intellectual disability
Oculo-Facio-Cardio-Dental	300166	*BCOR*	Xp11.4	X LD	Ocular defects (unilateral/ bilateral microphthalmia	Facial anomalies (narrow face with a broad nasal tip, separated nasal cartilage, cleft palate),
					Congenital cataracts	Congenital heart defects (septal defects),
						Skeletal anomalies.
						A diagnostic feature is dental root radiculomegaly
						Mild mental retardation
						Conductive or sensorineural hearing loss
Ohdo	249620			AR likely	Blepharophimosis	Mental retardation, congenital heart disease, teeth
				Other patterns of inheritance also possible		Cryptorchidism
						Cleft palate
						Bladder diverticulum
Oliver-McFarlane	275400	*PNPLA6*	19p13.2	AR	Long eye lashes	Intellectual disability
OMCS					Long eye brows	Sparse scalp hair
					Retinal pigmentary degeneration resembling choroideremia	Hypogonadism
						Micropenis
						Cryptorchidism
						Growth limitation
						Ataxia
						Titubation of the head
						Peripheral neuropathy

Ondine Curse	209880	*PHOX2B (Most common)*	4p13	AD	Anisocoria	Hirschsprung disease
		GDNF				Tumours of the neural
		RET				A characteristic box-shaped face is seen in patients with polyalanine repeat expansion mutations (PARMs).
		BDNF				Crest
		ASCL1				Hypoventilation during sleep
		EDN3				Near normal respiration during awake state
						Gastroesophageal reflux
						Constipation
						Hypotonia
						Hypothermia and thermal instability
						Alterations in blood pressure
						Autonomic dysfunction
Ophthalmo-Acromelic syndrome—OAS	206920	*SMOC1*	14q24.2	AR	Microphthalmia	Syndactyly of the fingers, metacarpal synostosis, polydactyly, fusion of carpal bones.
						Ectrodactyly
						Cryptorchidism
PHARC—Polyneuropathy Hearing loss Ataxia retinitis pigmentosa Cataract	612674	*ABHD12*	20p11.21	AR	Retinitis Pigmentosa	Pes cavus and Achilles tendon contractures
					Cataract	Hyporeflexia, hyperreflexia, extensor plantar responses, and neurogenic changes on EMG. Extensor plantar responses and cerebellar atrophy
						Ataxic and/or spastic gait disturbances progressive sensorimotor peripheral neuropathy.
						Hearing Loss
						Normal cognition
Pallister-Hall syndrome—PHS	146510	*GLI3*	7p14.1	AD	Coloboma	Common:
						Bifid epiglottis
						Hypothalamic hamartoma and hypopituitarism
						Polydactyly: Mesoaxial and postaxial polydactyly
						Y-shaped metacarpal or metatarsal bone
						Growth hormone deficiency and genital hypoplasia
Pearson	557000	N/A	N/A	Mitochondrial deletion/ duplications	Ptosis	Sideroblastic anemia
					Ophthalmoplegia	Pancreatic insufficiency
					Cataracts	Low birth weight, failure to thrive, hypoplastic anemia
					Pigmentary retinopathy	Renal impairment
Pierson	609049	*LAMB2*	3p21.31	AR	Microcoria and unreactive pupils	Congenital nephritic syndrome
					Hypoplasia of ciliary and papillary muscles	Hypotonia
					Lenticular anomalies	Neurodeveopmental defects

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Proteus	176920	*AKT1*	14q32.33	A mosaic somatic mutation of is seen in most patients.	Calcific band keratopathy	Dysmorphic facial features
					Abnormal vitreous structure chorioretinal hamartoma associated with serous retinal detachment vitreous hemorrhage	Dolichocephaly
					Myopia	Long face
					Cataract	Down slanting palpebral fissures and/or minor ptosis
						Depressed nasal bridge
						Wide or anteverted nares
						0pen mouth at rest
						Asymmetric overgrowth
						Gigantism, nevi, hemihypertrophy, and macrocephaly
						Partial gigantism
						Cerebriform Nevus,
						Lipoma
						Lung Cysts
						Intellectual disability
						Deep vein thrombosis
						Macrodactyly
						Cerebriform connective tissue nevi (CCTN)
						Linear verrucous epidermal nevus (LVEN)
						Hyperostosis of the skull
						Hyperostosis of the external auditory canal
						Megaspondylodysplasia
						Splenomegaly/thymus enlargement
Ramos-Arroyo	122430	*Not yet found*	Not yet found	AD	Hypoesthetic corneas	Dysmorphic facial features consisting of hypertelorism, flat Facial profile, Frontal bossing, depressed nasal bridge, and mid-facial hypoplasia
					Absence of peripapillary choriocapillaris and retinal pigment epithelium	Bilateral sensorineural hearing loss
						Persistent ductus arteriosus
						Moderate mental retardation
						Hirschsprung disease
Robert	268300	*ESCO2*		AR	Hypertelorism	Microcephaly
					Mid-facial capillary hemangioma	Intellectual disability
					Blue sclera	Cleft lip/cleft palate
					Corneal clouding	Limb anomalies usually all four limbs (upper limb>lower limb) Reduction in length of limbs
						Reduction in length or and number of digits
						Syndactyly, brachydactyly and Clinodactyly
						Flexion contractures
						Polycystic kidney disease
						Sparse silvery blonde scalp hair
						ASD/VSD/PDA
						Moyamoya

Robinow	268310 180700	*ROR2* *WNT5A*	9q22.31 3p14.3	AR AD	Hypertelorism	**Dysmorphic facial features:**
					Prominent eyes Down-slanting palpebral fissures	Broad forehead, prominent and widely spaced eyes, a short nose with an upturned tip, and a wide nasal bridge
					Rare: infantile glaucoma	Macrocephaly and Frontal bossing
						Skeletal abnormalities
						Shortening of the long bones in the arms and legs, particularly the forearms
						Brachydactyly, clinodactyly, dysplasia of nails
						Hemi-vertebrae leading to kyphoscoliosis
						Fused or missing ribs
						Short stature
						Small penis, clitoris, cryptorchidism,
						Triangular mouth and
						Down turned angles of the mouth
						Micrognathia
						Posteriorly rotated ears
Rubenstein-Taybi	180849 613684	*CREBBP* *EP300*	16p13.3 22q13.2	AD AD	High arched eyebrows	Dysmorphic facial features
					Long lashes	Characteristic grimacing/abnormal smile
					Refractive errors	Broad nasal bridge, beaked nose high arched palate, mild micrognathia, and
					Nasolacrimal duct obstruction/ malformation	Short stature
					Ptosis	Intellectual disability
					Epicanthus	Developmental delay
					Strabismus and nystagmus	Broad thumb and broad toe often angulated
					Glaucoma	Broad distal Phalanges
					Enophthalmos	Cryptorchidism
					Cataract	Congenital heart defects
					Coloboma	Constipation
						Talon cusps
						Sleep apnea syndrome
						Puberty and sexual development are normal
Russell-Silver	180860 312780	Uniparental disomy	7p11.2	AR X linked	Blue sclera	**Facial dysmorphism:**
					Refractive errors	Craniofacial features such as a triangular shaped face, Broad forehead and pointed, small chin with a wide, thin mouth.
					Subnormal stereoacuity	Intrauterine growth retardation, poor postnatal growth, body asymmetry.
					Remote near point of convergence.	Clinodactyly, camptodactyly
					Hypermetropia and anisometropia	Gastroesophageal reflux disease, esophagitis
					Smaller optic discs and tortuosity of retinal vessels.	Failure to thrive and aversion to food.

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Say-Barber	209885	*TWIST2*	2q37.3	AD	Telecanthus, ectropion	Facial dysmorphism:
					Partial or complete agenesis of the lids	Macrostomia, eyelid deformities, abnormal and low-set ears, bulbous nasal tip with hypoplastic nasal alae, and low frontal hairline
						Severe hypertrichosis,
						Hyper laxity and redundancy
						Macrostomia, atrophic skin, marked hypertrichosis, and growth retardation.
Schinzel-Giedion Midface Retraction	269150	*SETBP1*	18q12.3	AD	Alacrima	Severe mid-face retraction,
					Corneal hypoesthesia	Multiple skull anomalies (short and sclerotic base, multiple wormian bones, wide cranial sutures and fontanels)
						Short and sclerotic skull base, wide occipital synchondrosis, increased cortical density or thickness, or broad ribs
						Congenital heart defect
						Hydronephrosis
						Hypertrichosis
						Embryonal malignancy
						Choanal stenosis,
						Tricuspid regurgitation, hypospadias, Seizures, hearing loss, camptodactyly
						Mega ureter
Senior-Loken	266900	*NPHP1*	2q13	AR	Leber congenital amaurosis	Juvenile nephronophthisis
		NPNH2/INVS				Diabetes insipidus
	606955	*NPHP3*	3q22			
	606996	*NPHP4*	1p36			
	609254	*NPHP5*	3q21			
	610189	*NPHP6*	12q21			
	613615	*SDCCAG8*	1q44			
SHORT	269880	*PIK3R1*	5q13.1	AD	Telecanthus, deeply set eyes,	Intra Uterine Growth Retardation, developmental delay, delayed dental eruption,
Short Stature					Axenfeld-Rieger spectrum with or without	Sensory neural hearing loss, triangular facies, prominent ears, micrognathia
Hernia +/− Hyper-extensibility of Joints					Glaucoma	
Ocular depression						
Rieger anomaly						
Teething delay						

Sotos	117550	*NSD1*	5q35.2-35.3	AD	Astigmatism	Facial Dysmorphism:
					Cataract	Acromegaly like facial features High-arched palate and prominent jaw
					Strabismus	Large hands and feet
					Optic atrophy	Advanced bone age, Joint hypermobility
						Non-progressive cerebral disorder with mental retardation.
						Abnormal dermatoglyphics
						Hamartomatous polyps of the intestine
						Congenital heart defects
						Cryptorchidism, melanin spots of the penis
						Vertebral anomalies
						Absence of premolar tooth.
Townes-Brocks	107480	*SALL1*	16q21.1	AD	Less common:	Imperforate anus,
Renal-Ear-Anal-Radial syndrome (REAR)					Iris coloboma, microphthalmia, lamellar cataract, chorioretinal coloboma	Triphalangeal thumbs, fusion of metatarsals, absent bones, and supernumerary thumbs. sensorineural deafness
						Renal dysfunction
						Congenital heart disease
						Hypospadias, vaginal aplasia with bifid uterus, bifid scrotum, cryptorchidism
Traboulsi	601552	*ASPH*	8q12.3	AR	Ectopia lentis, micro spherophakia	Flat cheeks
					Iridocorneal adhesions	Beaked nose
					Iris atrophy	Retrognathia,
					Spontaneous subcutaneous filtering blebs	
Vanden Ende-Gupta syndrome (VDEGS)	600920	*SCARF2*	22q11.21	AR	Blepharophimosis	Triangular face, malar hypoplasia due to hypoplastic maxilla, narrow and beaked nose, everted lips,
						With or without cleft palate
						Thin ribs, hooked clavicles,
						Arachnodactyly
						Contractures that are usually self-limiting
						Ambiguous genitalia
						Retardation, microcephaly, failure to thrive, and severe joint limitation.
Warburg Micro syndrome-2	614225	*RAB3GAP2*	1q41	AR	Congenital cataract	Microcephaly, polymicrogyria, hypoplasia of the corpus callosum, and severe developmental delay
					Microphthalmia	

(continued)

Table 21.9 (continued)

Syndrome	MIM #	Genes	Loci	Inheritance	Ophthalmic manifestations	Systemic manifestations
Warsaw Breakage	613398	*DDX11*	12p11	AR	Optic disc coloboma	Facial dysmorphism
					Strabismus	Microcephaly (small and receding forehead, short nose, small nares, short neck, bilateral epicanthal folds, relatively large mouth, and cup-shaped ears) and high-arched palate
						Growth retardation,
						Hearing impairment,
						Ventricular septal defect, tetralogy of Fallot
						Hypotonia, Intellectual disability
						Single palmar crease, clinodactyly, syndactyly of toes,
						Abnormal skin pigmentation,
						Increased chromosomal breakage induced by mitomycin C, and premature chromatid separation.
Wolfram	222300	*WFS1*	4p16.1	AR	Optic atrophy (Onset before 16 years)	Diabetes Insipidus
(DIDMOAD)		*CISD2*	4q24		Usually after onset of diabetes mellitus	Diabetes Mellitus (usually the first to manifest)
						Sensory neural hearing loss
						Hypogonadism
						Cerebellar ataxia, peripheral neuropathy, dementia, psychiatric illness, and urinary tract atony)
						Delayed/absent puberty
						Non-autoimmune hypothyroidism
						Growth retardation

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