Recognizable Syndromes in the Newborn Period

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KEYWORDS

• Newborn period • Syndrome recognition • Dysmorphology • Birth defects

KEY POINTS

- Many syndromes have a different presentation in the newborn period compared with childhood or adult life, and recognition early in life is frequently based on a characteristic pattern of dysmorphic features and/or malformations that can vary from the classic presentation seen in childhood.
- Early recognition of syndromes is increasingly important, as for many of them there are professional guidelines for treatment and surveillance.
- Genetic testing with next-generation sequencing will increasingly be performed for diagnosis in the newborn period and will expand our understanding of the clinical variability within syndromes.

INTRODUCTION

The primary goals of the assessment of an infant with congenital anomalies in the neonatal period are to establish a diagnosis, identify associated abnormalities, develop a management plan, and assess the natural history and prognosis. The correct diagnosis enables parents and clinicians to obtain accurate information, plan for appropriate surveillance, determine recurrence risks and access support and advocacy groups. Standard tools for the diagnostic assessment in the newborn period include a pregnancy history, birth history and family history, physical examination, and investigations to delineate the presence of additional anomalies, including cranial ultrasound, chest radiograph, echocardiogram, abdominal or renal ultrasound, skeletal survey, and ophthalmologic examination. If the baby is stable, more detailed imaging or invasive testing, such as magnetic resonance imaging (MRI) scan of the brain or other relevant regions, can be considered.

Disclosures: none.
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Clin Perinatol 42 (2015) 263–280
http://dx.doi.org/10.1016/j.clp.2015.02.003 **perinatology.theclinics.com**
0095-5108/15/$ – see front matter

Chromosome testing with array comparative genomic hybridization (aCGH) is the standard of care in the investigation of many infants with multiple congenital anomalies, birth defects, or neurologic signs. Chromosomal aneuploidies and chromosomal deletions and duplications are identified in an estimated 7.5% of infants with multiple congenital anomalies. A growing number of infants also undergo gene panel sequencing or genomic testing with exome sequencing. Despite the increased testing options now available, an accurate knowledge of the presentation of syndromes in the neonatal period is often needed to obtain the correct diagnosis.

One of the most important initial decisions is whether an infant's presentation is syndromic, as opposed to an isolated birth defect or sequence that is less likely to be associated with additional malformations or an easily discernible underlying genetic cause. A syndrome can be defined as a set of developmental anomalies or pattern of defects occurring together in a recognizable and consistent pattern that is caused by a single cause.[1] Many syndromes are associated with dysmorphic features and a recognizable facial gestalt that enables a clinical diagnosis. Imaging or other investigations to determine the extent of phenotypic involvement and chromosomal, biochemical, and/or molecular genetic testing are usually performed to confirm the syndrome diagnosis. It is important to be aware that, just as the appearance and physiology of typically developing infants alters with time, the manifestations of syndromes can be specific to different developmental time periods. In the neonatal period, syndromes may either be more straightforward or more difficult to recognize. It is vital for clinicians to be aware of these differences, so that an age-appropriate differential diagnosis is considered at the baby's bedside.

This review describes a selection of the syndromes most frequently encountered in the newborn period, with an emphasis on the physical findings that present shortly after birth. The authors have focused on syndromes that are frequently encountered and that differ significantly in presentation in the newborn period compared with later in childhood, and on syndromes that are frequently encountered and for which early recognition is helpful because it prompts surveillance or more timely treatment. Space limitations have prevented the coverage of many conditions, and the craniosynostoses and disorders of sexual development that may present in the neonatal period are not included.

TEXT

Table 1 provides a summary of common syndromes that are recognizable in the newborn period based on cardinal symptoms and signs. Syndromes with causative genes have been grouped into body systems; syndromes caused by chromosome aberrations, metabolic conditions, and conditions with multifactorial or an unknown cause are listed separately. Genetic confirmation should be performed for those conditions for which it is available (Table 2), and it is important to remember that many chromosomal abnormalities can be phenocopies of Mendelian genetic syndromes. In the following text, the authors discuss selected conditions that have specific neonatal presentations, listing clinical features and reasons that an early diagnosis may be helpful.

CRANIOFACIAL SYNDROMES

The diagnosis of Van der Woude syndrome (MIM 119300) is a good example of the utility of a thorough examination, as the small lip pits that are pathognomonic for this condition in association with cleft lip/palate (CL/P) can sometimes be missed

(Fig. 1). Achieving a diagnosis in the neonatal period is important because of the autosomal dominant inheritance of this condition, which can result in a recurrence risk that is increased compared with the risks for isolated CL/P.[2] The lip pits can be surgically removed and, thus, may be less apparent at later ages.

Stickler Syndrome

Stickler syndrome (MIM 108300) classically presents with Pierre-Robin sequence (cleft soft palate with micrognathia) in the neonatal period. The diagnosis may be missed, as the ocular findings comprising vitreoretinopathy and retinal detachment, deafness, epiphyseal dysplasia, and degenerative joint disease may all be later manifestations.[3,4] A facial gestalt can aid recognition of Stickler syndrome in the newborn period and childhood, with infants demonstrating relatively prominent eyes and a flat facial profile with a hypoplastic midface and a short and anteverted nose, in addition to micrognathia (Fig. 2).[4] Stickler syndrome should also be considered in neonates with significant refractive errors, astigmatism, cataracts, and abnormal anterior chamber drainage that can predispose to glaucoma.[5] It is vital to distinguish Stickler syndrome from isolated Pierre-Robin sequence, as monitoring for the eye complications, such as retinal detachment, and prophylactic or early treatment can preserve vision. In addition, a cardiac assessment for complications, such as mitral valve prolapse, should be undertaken.

Stickler syndrome is an autosomal dominant condition with great variability, even within families; thus, a very careful family history may be an important diagnostic clue.[3] The condition is genetically heterogeneous, although most patients have mutations in the Collagen, Type II, Alpha-1 (*COL2A1*), Collagen, Type XI, Alpha-1 (*COL11A1*), and Collagen, Type XI, Alpha-2 (*COL11A2*) genes. A panel approach to genetic testing is frequently used (see Table 2).

SYNDROMES WITH HYPOTONIA

Prader-Willi Syndrome

Many infants present with hypotonia and feeding difficulties in the newborn period, and Prader-Willi syndrome [PWS; MIM 176270] should be considered in the differential diagnosis. PWS has an incidence of 1 in 10,000 to 1 in 15,000 individuals and a prevalence of up to 10% in a small series of infants with hypotonia.[6] The neonatal presentation of PWS includes central hypotonia that is frequently severe, leading to lethargy and feeding difficulties, with a weak suck and failure to thrive.[7] Dysmorphic features, such as bitemporal narrowing, almond-shaped palpebral fissures, and a thin upper lip, may also aid recognition in the newborn period.[7] Central sleep apnea has been described and may be ameliorated by oxygen therapy.[8] It is important to note that the classic features of truncal obesity and voracious appetite that develop later in childhood are absent in the neonatal period. Other features that are absent or less apparent in the newborn period include learning and behavioral differences, small hands and feet and short stature.[9,10]

PWS is caused by a variety of genetic mechanisms including paternal deletions at chromosome 15q11–15q13 (75% of patients), maternal uniparental disomy for this chromosome region (24% of patients) and imprinting defects (1% of patients). Diagnosis can be accomplished by determining methylation status of the small nuclear ribonucleoprotein polypeptide N gene (*SNRPN*; 99% yield). As therapy with growth hormone has been shown to be efficacious in normalizing the body habitus and lean body mass,[11] a timely diagnosis can help to prevent the complication of morbid obesity.

Table 1
Summary of selected syndromes that are recognizable in the newborn period: presentation

Syndromes	Characteristic Diagnostic Features	Differences in Presentation from Other Age Groups	Importance of Neonatal Diagnosis
Craniofacial Syndromes			
Van der Woude syndrome	CL/P, lip pits	No	Recurrence risk high
Stickler syndrome	Facial gestalt, Pierre-Robin sequence	Different dysmorphism	Screen for complications
Syndromes with Hypotonia			
Spinal muscular atrophy	Hypotonia	Severe in newborn	Appropriate care
Myotonic dystrophy	Respiratory difficulties	Severe in newborn	Screen for complications
Prader-Willi syndrome	Facial gestalt, hypotonia, FTT	FTT, no obesity	Early treatment
Cardiac Syndromes			
Noonan syndrome	Facial gestalt, cardiac defects, hypotonia, FTT	Different dysmorphism	Surveillance
Kabuki syndrome	Facial gestalt, cardiac defects, hypotonia	Different dysmorphism	Surveillance
Neonatal Marfan syndrome	Arachnodactyly, thin habitus; aortic dilatation	Different dysmorphism	Treatment of cardiac lesions
Gastrointestinal Syndromes			
Beckwith-Wiedemann	Macroglossia, macrosomia, abdominal wall defect	Severe in newborn	Screen for complications
Renal Syndromes			
WAGR	Wilms tumor, aniridia, genitourinary anomalies	No	Screen for complications
Skeletal Syndromes			
Achondroplasia	Facial gestalt, short limbs, short trunk	No	Screen for complications
Osteogenesis imperfecta	Multiple fractures, short stature, osteopenia	No	Early treatment
Syndromes with Skin Findings			
Incontinentia pigmenti	Multi-stage rash	Severe in newborn	Severe in newborn

Other Syndromes			
CHARGE syndrome	Coloboma, choanal atresia, heart defects	No	Screen for complications
Cornelia de Lange syndrome	Facial gestalt, limb defects	No	Screen for complications
Aneuploidy Syndromes			
Trisomy 21/18/13	See text	No	Screen for complications
Turner syndrome	Facial gestalt, cardiac defects, renal anomalies	Different dysmorphism	Screen for complications
Trisomy 8 mosaicism	Orthopedic manifestations	No	Screen for complications
Microdeletion Syndromes			
22q11 deletion syndrome	Outflow tract abnormalities, CP, hypocalcemia	Different dysmorphism	Screen for complications
William syndrome	Pulmonary stenosis, hypercalcemia, FTT	Different dysmorphism	Screen for complications
Smith-Magenis syndrome	Facial gestalt, cardiac manifestations	Different dysmorphism	Screen for complications
Metabolic Syndromes			
Smith-Lemli-Opitz syndrome	Facial gestalt, microcephaly, 2/3 syndactyly	No	Early treatment
Zellweger syndrome	Facial gestalt, hypotonia, liver disease, renal cysts	Different dysmorphism	Early treatment
Congenital adrenal hyperplasia	Ambiguous genitalia, salt wasting	No	Early treatment
Multifactorial/Environmental			
VATER/VACTERL	TEF, anal atresia, vertebral anomalies	No	Relatively good prognosis
Goldenhar syndrome	Facial asymmetry, microtia, epibulbar dermoids	No	Recurrence risk low
Infant of a diabetic mother	Macrosomia, sacral agenesis, multiple anomalies	—	Relatively good prognosis
Fetal alcohol syndrome	Facial gestalt, withdrawal syndrome	No	Screen for complications

Abbreviations: CHARGE, Coloboma-heart defects-atresia choanae-retardation of growth and development-genital defect-ear anomalies and/or deafness; CP, cleft palate; FTT, failure to thrive; NGS, next-generation sequencing; TEF, trachea-esophageal fistula; VATER/VACTERL, vertebral defects-anal atresia-cardiac anomalies-trachea-esophageal fistula-renal anomalies-limb defects; WAGR, Wilms tumor-aniridia-genitourinary anomalies-mental retardation.

Table 2
Summary of selected syndromes that are recognizable in the newborn period: inheritance and genetics

Syndromes	Inheritance	Genetic Cause	Testing Modalities
Craniofacial			
Van der Woude syndrome	Autosomal dominant	*IRF6* mutations	Sanger sequencing
Stickler syndrome	Autosomal dominant	*COL2A1, COL11A1, COL11A2* mutations	Panel/NGS approach
Central Nervous System			
Spinal muscular atrophy	Autosomal recessive	*SMN1* deletion/gene conversion; other genes	Deletion testing
Myotonic dystrophy	Autosomal dominant	*DMPK* trinucleotide repeat expansion	PCR/Southern blotting
Prader-Willi syndrome	Majority sporadic	Imprinting defect at chromosome 15q11	Methylation assay
Cardiac			
Noonan syndrome	Autosomal dominant	*PNPT11* mutations; other genes	Panel/NGS approach
Kabuki syndrome	Autosomal dominant	*KMT2D* mutations	Sanger sequencing
Neonatal Marfan syndrome	Autosomal dominant	*FBN1* mutations	Sanger sequencing
Gastrointestinal			
Beckwith-Wiedemann syndrome	Sporadic; autosomal dominant	Imprinting defect at chromosome 11p15	Methylation assay
Renal			
WAGR	Autosomal dominant	*WT1*/*PAX6* deletions	aCGH
Skeletal			
Achondroplasia	Autosomal dominant	*FGFR3* mutation	Sanger sequencing
Osteogenesis imperfecta	Autosomal dominant/recessive	*COL1A1* and *COL1A2* mutations; other genes	Panel/NGS approach
Skin			
Incontinentia pigmenti	X-linked dominant	*IKBKG* gene deletion/mutations	Deletion testing; Sanger sequencing

Other			
CHARGE syndrome	Autosomal dominant	*CHD7* mutations; other genes	Sanger sequencing
Cornelia de Lange syndrome	Autosomal dominant	*NIPBL* mutations; other genes	Panel/NGS approach
Aneuploidy Syndromes			
Trisomy 21/18/13	Majority sporadic	Trisomy 21/18/13	Karyotype
Turner syndrome	Sporadic	XO chromosome complement	Karyotype
Trisomy 8 mosaicism	Sporadic	Trisomy 8	Karyotype
Microdeletion Syndromes			
22q11 deletion syndrome	Autosomal dominant	22q11.2 microdeletion	aCGH
Williams syndrome	Autosomal dominant	7q11.23 microdeletion	aCGH
Smith-Magenis syndrome	Autosomal dominant	17p11.2 microdeletion	aCGH
Metabolic Syndromes			
Smith-Lemli-Opitz syndrome	Autosomal recessive	*DHCR7* mutations	Sanger sequencing
Zellweger syndrome	Autosomal recessive	*PEX* gene mutations	Panel/NGS approach
Congenital adrenal hyperplasia	Autosomal recessive	*CYP21A2* mutations; other genes	Sanger sequencing
Multifactorial/Environmental			
VATER/VACTERL	Sporadic	Not known	—
Goldenhar syndrome	Sporadic	Not known	—
Infant of a diabetic mother	Environmental exposure	NA	—
Fetal alcohol syndrome	Environmental exposure	NA	—

Abbreviations: CHARGE, coloboma-heart defects-atresia choanae-retardation of growth and development-genital defect-ear anomalies and/or deafness; NGS, next-generation sequencing; PCR, polymerase chain reaction; VATER/VACTERL, vertebral defects-anal atresia-cardiac anomalies-trachea-esophageal fistula-renal anomalies-limb defects; WAGR, Wilms tumor-aniridia-genitourinary anomalies-mental retardation.

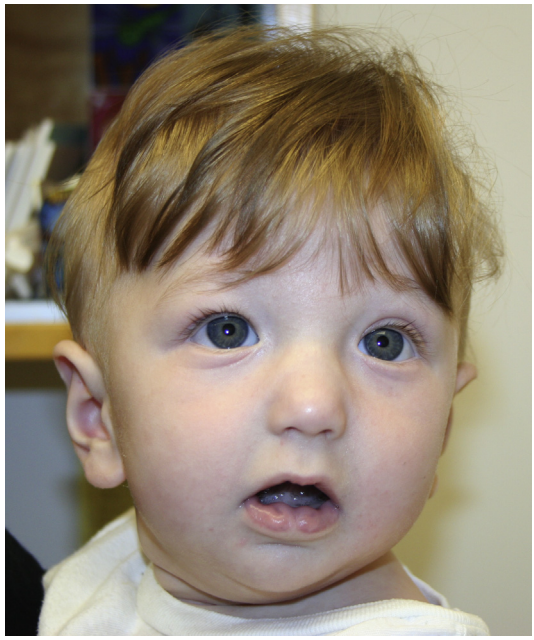

Fig. 1. Lip pits in Van der Woude syndrome. Frontal view of 13-month-old boy with a clinical diagnosis of Van der Woude syndrome, showing bilateral pits of the lower lip.

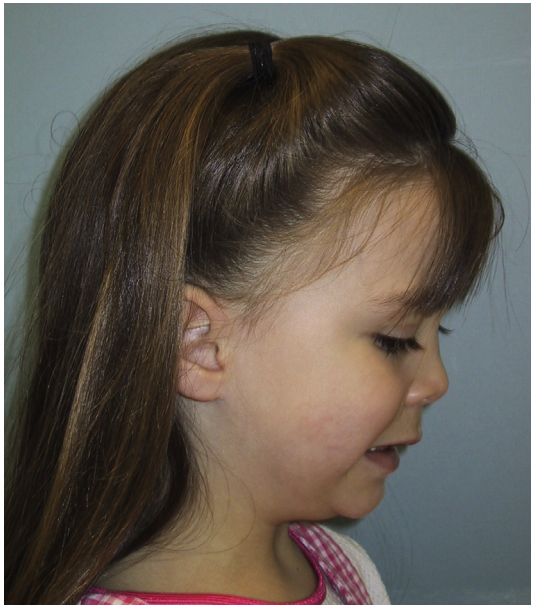

Fig. 2. Facial appearance of Stickler syndrome in childhood. Profile view of a 5-year-old girl with a clinical diagnosis of Stickler syndrome, showing midface hypoplasia, small and anteverted nares, and micrognathia.

Myotonic Dystrophy Type I

Myotonic dystrophy type 1 (MD1; MIM 160900) can manifest with a severe presentation in the neonatal period (congenital MD1), with hypotonia, respiratory difficulties, facial diplegia, talipes, joint contractures, and weak facial muscles resulting in a tented upper lip.[12] Other diagnostically useful findings include polyhydramnios and reduced fetal movements during pregnancy.[13] The condition can be critical, and death can result from respiratory insufficiency or cardiac failure.[13] In contrast to MD1 with a later onset in childhood, the pathognomonic finding of myotonia and the characteristic electromyogram abnormalities are absent,[14] making molecular genetic testing helpful for establishing the diagnosis.

Congenital MD1 is caused by an expanded CTG repeat in the dystrophia myotonica protein kinase (*DMPK*) gene, typically resulting from the unstable expansion of a large, maternally inherited allele.[12] As mothers may be more mildly affected, maternal history and physical examination for evidence of myotonia should be performed. It is critical to recognize this condition in the newborn period for appropriate management of the infant's care as well as for maternal health management and recurrence risk/family planning.

CARDIAC SYNDROMES

Noonan Syndrome and Disorders of the Ras Mitogen-Activated Protein Kinase (RasMAPK) Pathway

Clinicians may be alerted to the possibility of Noonan syndrome (NS; MIM 163950) or related disorders of the RasMAPK pathway (such as cardiofaciocutaneous syndrome, MIM 115151, or Costello syndrome, MIM 218040) in pregnancy because of polyhydramnios, increased nuchal translucency, and hydrops fetalis.[15] After delivery, many of the characteristic dysmorphic findings of NS are apparent; the facial appearance may be most obvious at this time, comprising a tall forehead with coarse facial features, ptosis with thick, droopy eyelids, hypertelorism with striking blue or blue-green irises, epicanthic folds, low-set and posteriorly rotated ears with thickened helices and a deeply grooved philtrum with high, and wide peaks to the vermillion border of the upper lip.[16] The neck may be short, with a low posterior hairline and excess nuchal skinfolds. Birth length and weight are typically normal in contrast to short stature and microcephaly that can develop in childhood.[16] Other findings that are frequent in neonates and serve as diagnostic indicators include cardiac defects, including neonatal hypertrophic cardiomyopathy[17], pulmonic stenosis and septal defects, and disordered lymphatic development that can manifest as lymphatic dysplasia,[18] lymphedema involving the dorsal surfaces of the hands and feet, and effusions.[19] Infants can also have marked hypotonia, joint hyperextensibility, and ulerythema ophryogenes (inflammatory keratotic facial papules).[20] Cryptorchidism may be a useful diagnostic finding in boys. Finally, infants with NS often have feeding difficulties and failure to thrive that improve in early childhood.

NS shows high genetic heterogeneity (ie, many different genes can cause NS and related disorders) (see **Table 2**), and testing with RasMAPK gene panels or exome sequencing is frequently used in preference to single gene testing. Early diagnosis can facilitate screening for other physical manifestations, monitoring for potential complications, such as prolonged bleeding caused by clotting factor deficiencies, and ensure that appropriate educational services and support are available.

Neonatal Marfan Syndrome

Neonatal Marfan syndrome is a severe but rare condition that is diagnosable on examination in the neonatal period based on the phenotypic findings of dolichocephaly, micrognathia, striking arachnodactyly with thin hands and feet, and loose and redundant skin. Cardiac abnormalities are almost universal and can include aortic dilatation and valvular insufficiency that can lead to early mortality.[21] Other neonatal findings include lens dislocation, rocker bottom feet, joint hypermobility of the fingers and toes, hypotonia, and pulmonary emphysema.[22,23] The later clinical manifestations contrast to children with fibrillin-1 (*FBN1*) mutations who present in childhood, in whom there may be no findings in the neonatal period.[24]

A phenotype genotype correlation has been proposed for *FBN1* mutations in Marfan syndrome, with mutations in exons 24 to 32 of the *FBN1* gene causing the neonatal phenotype[22]; but exceptions have been noted.[25] Recently, a related but novel syndrome with prematurity and accelerated linear growth compared with weight, a progerioid appearance, and congenital lipodystrophy resulting from mutations in the penultimate exon of *FBN1* was recognized.[26,27]

Coloboma, Heart Defects, Atresia of the Choanae, Retarded Growth and Development, Genital Abnormalities, and Ear Anomalies Syndrome

CHARGE is an acronym for coloboma, heart defects, atresia of the choanae, retarded growth and development, genital abnormalities, and ear anomalies. CHARGE syndrome (MIM 214800) should be considered in the newborn period whenever a combination of any of the aforementioned features is present. The aural malformations are particularly characteristic, with asymmetric, small, low-set ears that have overfolded or severely hypoplastic helices. CHARGE syndrome is an autosomal dominant condition that demonstrates extreme phenotypic heterogeneity; other clinical aids for recognition include microphthalmia, cranial nerve dysfunction with unilateral or bilateral facial palsy, cleft palate, and characteristic inner malformations including hypoplasia of the semicircular canals and Mondini malformation.[28] It is important to accurately diagnose CHARGE syndrome, as morbidity and mortality are high, with intellectual impairment that can be severe. The main causative gene, chromodomain helicase DNA-binding protein 7 (*CHD7*), demonstrates loss of function in an estimated 50% to 70% of individuals with the condition.[29] Recently, semaphorin 3A (*SEMA3A*) has been suggested to modify the function of *CHD7*; but mutations in this gene have so far been predominantly found in individuals with Kallmann syndrome rather than CHARGE syndrome and have accounted for less than 10% of *CHD7*-negative patients.[30]

GASTROINTESTINAL SYNDROMES

Beckwith-Wiedemann Syndrome

The cardinal features of Beckwith-Wiedemann syndrome (BWS; MIM 130650), including neonatal macrosomia, macroglossia, abdominal wall defects, and hypoglycemia, are most obvious in the newborn period. Other characteristic findings include ear lobe creases and ear pits of the posterior helix, intra-abdominal visceromegaly including nephromegaly, hemihyperplasia, and renal and cardiac defects.[31] The newborn facial appearance can also be characteristic, with nevus flammeus, infraorbital creases, and midface hypoplasia in addition to the macroglossia. BWS can be considered antenatally because of polyhydramnios and fetal overgrowth, and delivery can be premature. The incidence of BWS is estimated at 1 in 10,340 live births,[32] and the diagnosis should be readily considered and investigated in view of the cancer predisposition conferred by this syndrome.[33] Monitoring for malignancies, such as Wilms

tumor and hepatoblastoma, should start immediately after clinical diagnosis, as aggressive tumors have been described in the neonatal period.[32,34]

BWS is caused by epigenomic and genomic alterations on chromosome 11p15 that are found in up to 80% of affected individuals, including maternal microdeletions of imprinting centers 1 and 2 and paternal uniparental disomy and microduplications.[31] A link between BWS and assisted reproductive technologies was proposed, but this has not been confirmed in all studies.[35,36]

SYNDROMES WITH SKIN FINDINGS

Incontinentia Pigmenti

Incontinentia pigmenti (IP; MIM 308300) is a rare but highly diagnosable skin condition that most frequently commences in the neonatal period with blisters along the lines of Blaschko on the limbs and trunk, progressing through verrucous lesions, streaky lines of hyperpigmentation, and pale, atrophic streaks in childhood to adult life.[37,38] Neurologic complications include cognitive differences, seizures and microcephaly, and cerebral infarcts; brain atrophy and abnormalities of the corpus callosum have been noted on brain imaging.[39] Dental findings include hypodontia and microdontia; sparse hair, nail dystrophy, and retinal lesions may also be observed. The diagnosis is important to recognize in the newborn period, as the skin lesions may be less pronounced and harder to diagnose with certainty in childhood and adult life. IP is caused by loss-of-function mutations in the X-linked dominant inhibitor of kappa B kinase gamma (*IKBKG*) gene; a recurrent intragenic deletion involving exons 4 to 10 of *IKBKG* is found in most affected individuals.[38]

Goltz Syndrome

Goltz syndrome, also known as focal dermal hypoplasia (MIM 305600), can be diagnosed by skin lesions comprising patchy dermal hypoplasia, hyperpigmentation and hypopigmentation, fat herniation, and papillomas that manifest along Blaschko's lines and that are usually accompanied by digital (oligodactyly, ectrodactyly, syndactyly), ocular (microphthalmia, coloboma, cataracts), and dental abnormalities.[40] This condition is an X-linked dominant disorder caused by mutations in the Porcupine, Drosophila, Homolog-of (*PORCN*) gene that was considered fatal in boys and diagnosable only in males with mosaicism, Klinefelter syndrome, or a hypoplastic mutation.[41,42] The classic dermatologic findings can be present in the newborn period and confirmed on skin biopsy or mutation analysis, thus enabling a diagnosis and monitoring for other complications.

ANEUPLOIDY SYNDROMES

Trisomy 21: Down Syndrome

Although rarely missed, the diagnosis of trisomy 21 is important to achieve in the neonatal period, as specific management guidelines for health complications are available.[43,44] Infants with Down syndrome have a characteristic appearance that is familiar to many, with a flat facial profile, brachycephaly, excess skin at the back of the neck, upslanting palpebral fissures with epicanthic folds, small ears with overfolding of the upper helix, diminished middle phalanges of the fifth fingers, single transverse palmar creases, and a wide sandal gap between the first and second toes. These infants also have brachycephaly, mild microcephaly, late closure of fontanelles, Brushfield spots and peripheral iris hypoplasia, a small nose with a low nasal bridge, and a short hard palate. Joint hyperextensibility, an absent Moro reflex, and a

dysplastic pelvis on radiographs are all frequent. The overall appearance is that of a hypotonic infant with an open mouth and a protruding tongue.

Infants with Down syndrome have a 50% incidence of congenital heart disease (CHD), with atrioventricular septal defect, ventricular septal defect, atrial septal defect, patent ductus arteriosus, overriding aorta, tetralogy of Fallot, and an aberrant subclavian artery among the commonly encountered lesions. Pulmonary hypoplasia may cause breathing difficulties independently from CHD. Duodenal stenosis/atresia and Hirschsprung disease are also seen. All individuals with Down syndrome have delayed growth, and measurements should be plotted on specific Down syndrome growth charts. These children are at risk for hearing loss that is exacerbated by serous otitis media and for cataracts, strabismus, nystagmus, and myopia.

Investigations should include a chest radiograph, electrocardiography, and echocardiography within the first month of life. A complete blood count should be performed to rule out hyperviscosity syndrome and transient myeloproliferative disorder, which has a 10- to 30-fold greater incidence in individuals with Down syndrome, as compared with the general population.[45] Transient megakaryocytic leukemia can be found in 10% of newborns with Down syndrome caused by specific mutations of Gata-binding protein 1 (*GATA1*). Newborns must also be screened for hypothyroidism, and all infants should be referred to early intervention services.

Ninety-five percent of individuals with Down syndrome have 3 free copies of chromosome 21 resulting from meiotic non-disjunction; but 3% to 4% of cases are caused by unbalanced translocations involving chromosome 21, and 1% are caused by mosaicism, making this one of the chromosomal conditions whereby a karyotype, rather than aCGH is indicated.

Trisomy 18 and Trisomy 13

These aneuploidies are important to diagnose promptly because of the likelihood of reduced survival, which can influence medical and surgical management decisions.[46] In trisomy 18, the 3 most common neonatal findings are clenched hands with overlapping fingers, rocker bottom feet, and low-set or malformed ears.[47] A newborn with trisomy 18 will typically be small for gestational age, with a prominent occiput, and a short sternum. Other major clinical features include hypertonia, anteroposterior elongation of the skull with a prominent occiput, micrognathia, CHD, a narrow chest with a short sternum, renal anomalies, and partial syndactyly of the toes with hypoplastic nails.[48] In trisomy 13, presentation is notoriously variable; one study found ear anomalies, CL/P, and heart disease to be the most common manifestations.[49] However, postaxial polydactyly and the appearance associated with holoprosencephaly, including microcephaly, microphthalmia, and hypotelorism, have also been considered hallmarks of this condition. Other physical findings in newborns with trisomy 13 include cutis aplasia of the scalp (may be confused with lacerations), omphalocele, genital abnormalities (including cryptorchidism and micropenis), cystic kidneys, and capillary hemangiomata.[50]

In most patients with trisomy 18 and 13, a full copy of the extra chromosome is present. However, mosaicism and translocations can occur; a karyotype is, therefore, recommended over aCGH.

MICRODELETION SYNDROMES

22q11 Deletion Syndrome

The 22q11.2 deletion syndrome (also known as diGeorge syndrome [MIM 188400] and velocardiofacial syndrome [MIM 192430]) is the most common microdeletion

syndrome, with an incidence of 1 in 4000 births.[51,52] The 22q11.2 deletion syndrome is often diagnosed in the newborn period because of characteristic malformations, as the commonly recognized facial appearance is not always present. The malformations associated with 22q11 deletions include submucous cleft palate, bifid uvula and conotruncal heart defects, with right-sided aortic arch, tetralogy of Fallot, aberrant left subclavian artery and ventricular septal defect, neonatal hypocalcemia caused by hypoparathyroidism, and abnormal T-cell function caused by thymic hypoplasia. In infancy, the only notable dysmorphic features may be atypical ears, an anteverted nose, and microretrognathia. Later in childhood, the narrow palpebral fissures, prominent nose, squared nasal root and narrow alar base, and malar hypoplasia become more obvious, in addition to hypernasal speech and speech delay. Other common findings in infancy include hypotonia and microcephaly.

Recommended investigations include an electrocardiogram and echocardiogram; ionized calcium level; baseline immune profile; renal sonogram and cardiology, ear, nose and throat, and audiology and immunology consultations. The typical 3 megabase microdeletion at 22q11.2 contains an estimated 60 genes and is found in 90% of cases.[51] The deletion is caused by non-allelic homologous recombination between low-copy number repeats.[51] The diagnosis can be made by fluorescence in-situ hybridization (FISH) or aCGH.

Williams Syndrome

In the newborn period, the diagnosis of Williams syndrome (also known as Williams-Beuren syndrome; MIM 194050) can be suggested by a cardiologist following detection of the classic cardiac lesions of supravalvular aortic stenosis, peripheral pulmonary artery stenosis, pulmonic valvular stenosis, and supravalvular pulmonic stenosis. Persistent hypercalcemia is an additional sign that is diagnostically useful early in life. In contrast to the presentation in early childhood, the characteristic dysmorphic features of periorbital puffiness and full lips may be harder to recognize in the neonatal period, or the dysmorphic features may be non-specific. These newborns also manifest joint hypermobility and soft lax skin.[53] Renal anomalies, including nephrocalcinosis, asymmetry in kidney size, small solitary or pelvic kidney, bladder diverticulae, urethral stenosis, and vesicoureteral reflux, are also common.[54] Williams syndrome is caused by a deletion at 7q11.23, causing hemizygosity for the elastin gene[55] that is detectable either by FISH or aCGH.

METABOLIC SYNDROMES

Smith-Lemli-Opitz Syndrome

The phenotype of Smith-Lemli-Opitz (SLO) syndrome can be noticeable in the newborn period because of associated malformations, including cleft palate, cardiac defects with atrioventricular septal defects and total anomalous pulmonary venous drainage, hypospadias and cryptorchidism, postaxial polydactyly, and short thumbs.[56] The facial appearance may also be suggestive because of microcephaly, ptosis, a depressed nasal bridge, and a short and anteverted nares with micrognathia. Particularly pathognomonic is Y-shaped syndactyly of the second and third toes.[56] Although rare, recognition of SLO is critical because the biochemical pathway is well understood and multiple treatment options with cholesterol, statins, antioxidants, and gene therapy exist, although data from randomized controlled trials documenting improvement after therapeutic modalities are scarce.[57]

SLO syndrome is an autosomal recessive condition caused by deficiency of the enzyme 7-dehydrocholesterol reductase, leading to low cholesterol and elevated

serum levels of 7- and 8-dehydrocholesterol that can be assayed to establish the diagnosis.[58] Genetic testing for 7-dehydro cholesterol reductase (*DHCR7*) gene mutations is also clinically available.

SYNDROME OF UNKNOWN CAUSE

Vertebral Defects, Anorectal Malformations, Cardiac Defects, Tracheoesophageal Fistula, Esophageal Atresia, Renal Anomalies, and Limb Deformities

VATER/VACTERL association (vertebral defects, anorectal malformations, cardiac defects, tracheoesophageal fistula, esophageal atresia, renal anomalies, and limb deformities) is a non-random association that has been well established. Prevalence has been estimated at 1 in 10,000 to 1 in 40,000.[59] The characteristic pattern of anomalies aids recognition in the newborn period; the diagnosis is important, as VATER/VACTERL is a sporadic condition and generally without implications for abnormal growth or developmental progress.[59,60] aCGH is frequently performed because the differential diagnosis may be broad; but the cause of this condition is unknown, and the mainstay of management is surgical with long-term care related to the underlying malformations.

Hemifacial Microsomia

Hemifacial microsomia (also known as Goldenhar syndrome, oculoauriculovertebral dysplasia, and craniofacial microsomia; MIM 164210) is diagnosed at birth in around two-thirds of cases, with the most frequent phenotypic findings comprising microtia, facial asymmetry or hemifacial microsomia, and ear tags.[61] It is important to consider this diagnosis because of the clinical variability and high prevalence (69.5%) of malformations in other organ syndromes, including cardiac defects.[61] The pathogenesis has been hypothesized to include both environmental (for example, maternal diabetes) and genetic factors but remains unknown in almost all cases.

SUMMARY/DISCUSSION

The authors provide brief descriptions for some of the most common syndromes that present in the newborn period, outlining the differences between presentations in the newborn period and those at later ages for selected conditions. Phenotypes may be more severe (for example, neonatal Marfan syndrome, congenital myotonic dystrophy, and IP) or less fully developed (for example, Stickler syndrome). Early recognition is important for specific surveillance (for example, BWS and Stickler syndrome) or for starting treatment (for example, SLO). Many syndromes can be recognized from a typical pattern of malformations in the newborn period (for example, 22q11 deletion syndrome and VATER/VACTERL).

Most of these conditions have cardinal manifestations and natural histories that were defined long in advance of current clinical practices. However, the growing availability of information continues to refine management; efforts to remain abreast of changes in the literature are increasingly important. Finally, the landscape of genetic testing has changed dramatically with the introduction of next-generation sequencing technologies, such as whole-exome or whole-genome sequencing; it is likely that these methodologies will be increasingly used in the newborn period.[62] Exome sequencing has resulted in an expansion of the clinical features connected with the phenotype for many different disorders; although less applicable to the common syndromes described earlier, it is likely that this test will substantially influence how clinicians approach syndrome diagnosis in the newborn period for rarer diseases in the future.

Best Practices

What is the current practice?

Many syndromes have a different presentation in the neonatal period compared with later in life. Most children with multiple anomalies undergo tests, such as cranial ultrasound, chest radiograph, echocardiogram, abdominal or renal ultrasound, skeletal survey, and ophthalmology examination, to define the extent of their anomalies. If the baby is stable, more detailed imaging or invasive testing, such as MRI of the brain or other relevant regions, can be considered. Chromosome testing with array comparative genomic hybridization is also commonly performed as an initial screening test.

Best practice/guideline/care path objectives

What changes in current practice are likely to improve outcomes? The introduction of next-generation sequencing technologies (for example, exome sequencing) is likely to increase diagnostic yield in the neonatal period.

Summary statement

It is important for clinicians to be aware that the presentation of common syndromes can vary with age. It is likely that exome sequencing will be increasingly used in diagnostic investigations in the newborn period in the future.

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