Assessment of the dysmorphic infant

Malformation can be an isolated event, but some infants have multiple malformations and in many cases these will have a single underlying cause. Malformations which tend to occur in association with each other often form recognisable patterns or syndromes. Recognition of syndromic patterns in infants can provide parents and professionals with important information which may influence management and inform prognosis and natural history.

Jill Clayton-Smith
MBChB, FRCP, MD
Professor of Medical Genetics, St Mary's Hospital, Manchester
jill.clayton-smith@cmmc.nhs.uk

Keywords

malformation; syndrome; dysmorphic features; genetic counselling

Key points

Clayton-Smith J. Assessment of the dysmorphic infant. *Infant* 2008; 4(6): 206-10.

1. One in 40 babies are born with a birth defect.
2. Malformation syndromes may have an underlying genetic basis, may be multifactorial or may be due to an environmental cause.
3. Recognition of a syndrome may influence management, inform prognosis and enable accurate recurrence risks to be given for future pregnancies.
4. Information from post-mortem examination may provide vital clues to a diagnosis.
5. Storage of a DNA sample, with consent, should be considered where the diagnosis is not immediately apparent and prognosis is uncertain.

One in 40 infants are born with a malformation. This may be an isolated malformation or may occur together with other malformations and/or dysmorphic features as part of a malformation syndrome. Around 4,000 malformation syndromes have now been delineated[1,2]. Many are associated with medical problems and making a specific syndrome diagnosis can influence immediate medical management e.g direct screening for known complications. Making a syndrome diagnosis can also be important for parents seeking information about their child's diagnosis and prognosis. In addition it facilitates accurate genetic counselling for the parents and their extended family if future pregnancies are planned.

Even in situations where the infant may not survive, having a syndrome diagnosis is important as it can guide diagnostic investigation and influence management of the severely ill neonate. In the event of a neonatal death it can direct storage of appropriate tissue samples, and provide useful information for a paediatric pathologist carrying out a post mortem examination. Making a syndrome diagnosis is often regarded as a mysterious process, but it essentially follows the same steps as for any other clinical diagnosis. An overview of the diagnosis of patients with dysmorphic features has been outlined in various texts[3,4]. This article summarises the approach to be taken when assessing the infant with malformations and provides a simple checklist to use in this situation (**TABLE 1**).

History

Many clues to the aetiology of dysmorphic features and malformations can be obtained from a good family and pregnancy history. Drawing up a detailed three generation family history may identify similarly affected family members or demonstrate a clear Mendelian pattern of inheritance. Recurrent miscarriages may suggest that parents are carriers of a chromosomal imbalance. Enquiry should be made about maternal disease such as diabetes mellitus and any medication taken during pregnancy, eg antiepileptic drugs. A history of maternal alcohol or recreational drug exposure may also be relevant. Severe hyperemesis has been linked with dysmorphic facial features and skeletal abnormalities.

Ultrasound scans during pregnancy may show specific fetal malformations or may be more general indicators of a syndrome diagnosis; the finding of nuchal oedema on scan or of choroid plexus cysts may raise the possibility of a chromosome disorder, for example. Severe oligohydramnios can predispose to congenital contractures and dysmorphic features consistent with oligohydramnios sequence (Potter's syndrome). Some syndromes are associated specifically with intra-uterine growth retardation and others with fetal overgrowth. Mechanical constraint caused by uterine abnormalities eg bicornuate uterus can lead to fetal deformation and explain an unusual head shape or the presence of talipes deformity.

Examination for dysmorphic features

As with any neonatal examination, it's important to keep the baby warm during examination, to wash the hands carefully beforehand and not to disturb any equipment if the baby requires ventilatory support or monitoring. However, it is particularly important for the dysmorphologist to try to see as much of the baby as possible and if clothing, tape or

1. **General information**	Name Sex Date of birth Ethnicity
2. **Family history**	Three generation pedigree Enquire about consanguinity
3. **Pregnancy history**	Obstetric complications Maternal illness, eg diabetes Exposures, eg alcohol, medications Abnormal investigations (scan, serum screening, amnio, CVS) Liquor volume Abnormal lie
4. **Birth history**	Gestation Mode of delivery Placenta and cord vessels Apgars Birth weight Malformations noted at birth Admission to special care unit
5. **Neonatal period**	Feeding Complications, eg jaundice, respiratory
6. **General examination**	Handling Skin pigmentary anomalies Oedema, nuchal or general
7. **Dysmorphic features**	Skull shape, sutures, fontanelles Facial features Ear shape and position Eye spacing, red reflex, coloboma Body proportions and symmetry Chest shape and nipples Abdominal wall Spine, sacral anomalies or appendage Limbs – length, bowing, contractures, joint laxity Digits, number and shape Palmar creases – fetal pads Genitalia and anal anomalies
8. **Neurodevelopmental**	Muscle tone and power Focal neurological signs Movements Appropriate development in older infants
9. **Investigations**	Ultrasound of abdomen, heart, brain MRI if indicated (abnormal scan, head size, seizures) Skeletal survey if bone dysplasia suspected Routine haematology and biochemistry Metabolic Cytogenetic Molecular genetic
10. **Photographs**	Obtain parental consent Position main dysmorphic features against a plain background
11. **Following assessment**	Document findings in notes and for parents Discuss with parents Make clear plans for investigation and follow-up

TABLE 1 A checklist for assessment of the dysmorphic infant.

equipment obscures the face or other parts of the body, a return visit will be required. All clothing and the nappy should be removed if possible prior to examination. In preterm infants it is important to be familiar with the normal physical signs associated with prematurity so that these are not interpreted as dysmorphic features e.g. soft ear cartilage causing an unusual shaped pinna. The ethnic origin of the infant must be taken into consideration when assessing skin colour, facial features and the presence of hirsutism.

Observation

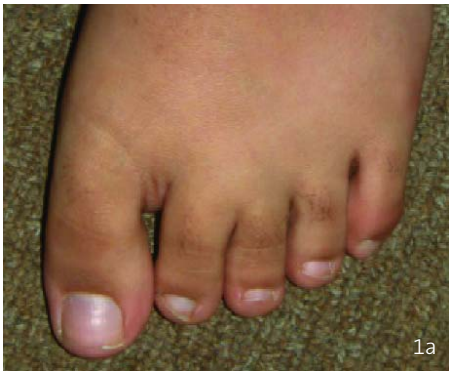
Initial observation will enable assessment of the general body habitus and demonstrate postural abnormalities such as the characteristic hand posture of Trisomy 18 or the slender body habitus and contractures of neonatal Marfan syndrome. Abnormal body proportions may be apparent, eg in achondroplasia where the presence of extra skin creases in the limbs is a consequence of shortening of the femora and humeri. A frog-like posture suggests severe hypotonia, the differential diagnosis of which includes Prader-Willi syndrome, congenital myotonic dystrophy, myopathy or a metabolic disorder. The overall facial gestalt may suggest a diagnosis even at this stage, eg in Cornelia De Lange syndrome. Silvery white hair may lead to an instant diagnosis of oculocutaneous albinism.

Examination

Routine growth parameters should be measured and plotted on the appropriate charts[5]. Measurement of occipitofrontal circumference can be problematic in neonates if there is a significant amount of moulding and it is worth repeating this again after a few days. A routine general examination, usually beginning at the head and working downwards, will reveal most major malformations. A specific search must be made for minor malformations and dysmorphic features. For a comprehensive approach to examination readers are encouraged to consult the text by Aase et al[6].

The skull should be examined for overall shape and any ridging of the sutures indicative of craniosynostosis. The presence of any scalp defects (a good marker for Trisomy 13) and unusual hair patterning should be noted. Facial features are often difficult to assess in neonates and may change day by day. They may be altered significantly in the presence of oedema and have to be considered in the context of the family features and so it is useful to see the parents and any siblings.

Limb defects and digital abnormalities should be described accurately as they can be of great help in drawing up a differential diagnosis. Some syndromes are associated only with pre-axial polydactyly with duplication of the thumbs or great toes, for



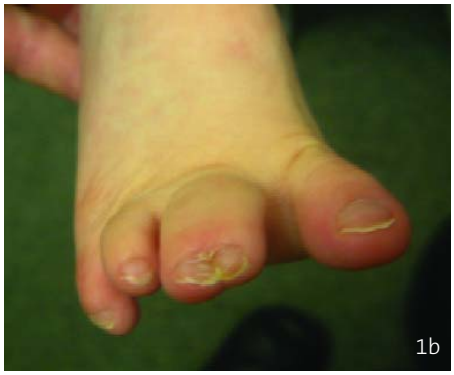


FIGURE 1 Partial 2/3 syndactyly (1a) is a normal variant and is not usually of any consequence whereas complete 2/3 syndactyly (1b) is more significant.

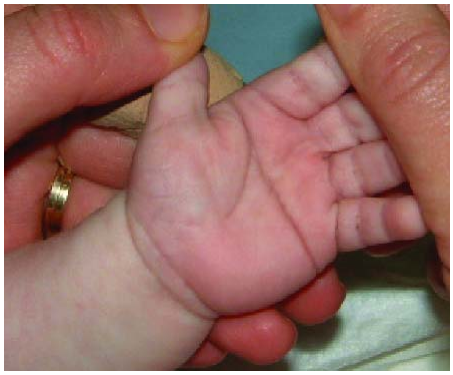


FIGURE 2 A single palmar crease is found in 4% of the general population and is bilateral in 1%.

instance, whereas post-axial polydactyly is commoner and can be an isolated finding. The pattern of any missing digits or syndactyly should be documented, remembering that partial 2/3 syndactyly is a normal variant, but complete or Y-shaped 2/3 syndactyly is more significant (**FIGURE 1**).

Abnormalities of the palmar creases may indicate that the hands have not moved properly during fetal life and suggest a neurological problem, but a single palmar crease may be a normal variant and present in other family members (**FIGURE 2**). Genitalia should be examined for any ambiguity, placement of the anus noted and enquiry made as to whether the baby has passed urine and meconium normally. Any skin lesions or naevi and their distribution should be documented. Skin lesions which follow Blaschko's lines down the limbs and around the trunk, such as the blistering lesions of incontinentia pimentii, are often indicative of mosaicism and more common in females with X-linked dominant disorders. Subtle alterations in pigmentation may not become apparent until the skin thickens after the neonatal period. In families where skin colour is darker, it is normal to find some uneven skin pigmentation, particularly around the axillae and groins. If you have parental consent, take a photograph of the baby to document the most significant dysmorphic features. This can help remind you of the features in your search for a diagnosis and provide a valuable record of the natural history of the condition.

Condition	Presenting features	Diagnostic test
Trisomy 21 Down syndrome	Brachycephaly, simple ears, hypotonia, AVSD, single palmar crease, sandal gap, Hirschsprung disease	Karyotype or QFPCR shows trisomy 21
Trisomy 18 Edwards syndrome	Contracture of fingers, globular head, dysplastic ears, low birth weight, heart defects, short great toes, radial aplasia	Karyotype or QFPCR shows trisomy 18
Trisomy 13 Patau syndrome	Holoprosencephaly, cleft , heart defect, polydactyly, renal abnormalities, microphthalmia	Karyotype or QFPCR shows trisomy 13
4p- Wolf-Hirschorn syndrome	Hypertelorism, prominent glabella (Greek helmet), cleft lip and palate, short philtrum, large ears	May be visible on routine karyotype. More reliably detected by FISH or MLPA
5p- Cri du Chat syndrome	Mewing cry, microcephaly, round face, prominent epicanthic folds, cleft palate, ear anomalies	Deletion of 5p15 usually visible on routine karyotype. FISH will detect smaller deletions
12p tetrasomy Pallister Killian syndrome	High birth weight, macrocephaly, diaphragmatic hernia, coarse face, hypotonia, long philtrum, sparse hair over temples	Always in mosaic form. Unlikely to be detectable on blood chromosome analysis. Need skin biopsy or FISH cells from buccal mucosa
22q11 deletion Di George syndrome Velocardiofacial syndrome	Cardiac defects especially outflow tract. Cleft palate, micrognathia, prominent nose, overturned helix of ear, hypocalcaemia, absent thymus	FISH for 22q11 deletion Few have smaller deletions detectable on MLPA of 22q11

KEY *QFPCR – Quantitative fluorescence polymerase chain reaction, a DNA-based test for gene dosage*
FISH – Fluorescence in-situ hybridisation
MLPA – Multiplex ligated probe amplification, a DNA-based test for gene dosage
AVSD – Atrio-ventricular septal defect

TABLE 2 Chromosomal abnormalities presenting in the neonate.

Behavioural features

The baby's general muscle tone, movements and behaviour should be noted as some syndromes have specific behavioural phenotypes. The cat-like cry of Cri du Chat (5p-) syndrome, the feeding difficulties and hypotonia of Prader-Willi syndrome and the panting respiration and apnoeas seen in Joubert syndrome are good examples. In those infants where the diagnosis of Down syndrome is being considered, hypotonia is a good pointer towards the diagnosis and there are often subtle snake-like movements of the tongue as it protrudes between the lips.

Specialist opinions

There are many occasions when a specialist opinion should be requested. When examining the eyes, for instance, obvious ocular anomalies such as anophthalmia, cataract with absence of the red reflex, glaucoma with enlarged and bulging corneas and iris coloboma may be noted by the paediatrician, but an

Condition	Presenting features	Investigation
Prader-Willi syndrome	Neonatal hypotonia Bitemporal narrowing Almond-shaped eyes Tube feeding required	DNA for 15q11-13 methylation (15q11-13 FISH will miss infants with uniparental disomy (UPD)of chromosome 15)
Myotonic dystrophy	Hypotonia Tented upper lip Elevated diaphragm Mother has myotonia	Examine mother DNA for expansion in myotonic dystrophy gene on chromosome 19
Beckwith-Wiedemann syndrome	Exomphalos High birth weight Large tongue Facial naevus flammeus	DNA to assess methylation of 11p15 Parental DNA for UPD studies. Not all have 11p abnormality
Cornelia De Lange syndrome	Low birth weight Synophrys, hirsutism Beaked philtrum Heart defects. Limb defects but may be subtle Diaphragmatic hernia	Primarily a clinical diagnosis. Some have mutations in NIPBL gene on chromosome 5 or other genes. Genetic abnormality not found in every patient
Neonatal Marfan syndrome	Long limbs, arachnodactyly, contractures, enophthalmos, dislocated lenses, wrinkly skin, heart murmur	Cardiac echo and follow-up as aortic dilatation may not be present at birth. Eye examination, FBN1 mutation analysis
Rubinstein-Taybi syndrome	Broad, medially deviated thumbs and great toes, long columella, hirsutism, microcephaly, heart defects, glaucoma	Clinical diagnosis FISH 16p13 deletion in 15-20% Some have mutations in CRBBP gene. Many have no genetic abnormality identified
Goldenhar syndrome (Hemifacial microsomia)	Findings usually unilateral. Mandibular hypoplasia, dysplastic or absent ear, pre-auricular tags, macrostomia, epibulbar dermoid. May be vertebral and cardiac defects	Clinical diagnosis Heterogeneous condition with both genetic and environmental causes
Achondroplasia	Proximal limb shortening, relatively large head, trident hand, extra skin creases, depressed nasal bridge, lumbar kyphosis	Skeletal survey shows square ilia, translucent proximal femur, narrow sacrosciatic notch. Analysis of FGFR3 gene shows characteristic mutation
Stickler syndrome	Pierre Robin sequence with cleft palate and micrognathia. Flat nasal bridge, prominent eyes, joint laxity	Eye examination shows myopia and vitreous abnormalities (not often apparent at birth). Mild platyspondyly on spinal X-ray. Genetic testing complex May be mutation in Type 2 or Type 11 collagen genes

TABLE 3 The commoner syndrome diagnoses made in infancy.

ophthalmological opinion should be sought if there are concerns about more subtle abnormalities or abnormal vision or eye movements. A neurological opinion is important when assessing those babies with abnormal muscle tone, movements or contractures and the input of the metabolic team can be invaluable in managing babies who present with profound hypotonia, seizures, bio-chemical abnormalities such as persistent acidosis, or worsening neurological status.

Investigations

In some cases where the history and clinical features suggest a specific syndrome diagnosis, it will be possible to order a confirmatory test, eg a chromosome analysis in suspected trisomy 18; methylation analysis of chromosome 11p in Beckwith Wiedemann syndrome; or a search for a gene mutation in known single gene disorders. In those patients where the diagnosis is unknown a series of screening investigations are usually carried out, including routine haematology and biochemistry. Chromosome analysis should be carried out in infants who have more than one major or minor anomaly or dysmorphic features. Babies with congenital heart disease should also be screened for a microdeletion of chromosome 22q11. Any infant with a suspected skeletal dysplasia will need a good quality skeletal survey, not forgetting X-rays of the hands and feet which often provide vital clues. In infants with more than one malformation externally, a search should always be made for internal malformations and this should include an echocardiogram, a renal ultrasound and a cranial ultrasound. If the latter is abnormal cranial MRI will provide more information. **TABLES 2 and 3** list some of the commoner dysmorphic syndromes diagnosed at birth and the diagnostic investigations involved.

Arriving at a diagnosis

It may be possible to make a 'gestalt' diagnosis in infants where the facial features are distinctive. In other cases, careful consideration of the information gained from the history, examination and investigation may help to narrow down the differential diagnosis and direct further investigations. Involvement of a clinical geneticist with expertise in paediatric dysmorphology is recommended since many disorders are individually rare. A search of the relevant literature and dysmorphology databases such as the London Medical Database[1], using the most specific diagnostic features as search handles, may help the clinician to arrive at a diagnosis.

Where the diagnosis is not made immediately, review is essential as facial features change with age and only after follow-up will it be possible to assess growth and development. It is important not to label a child with a syndrome diagnosis if the diagnosis is not certain. It

is far better to wait and review the diagnosis when the baby is older or seek another opinion from an expert.

Following the diagnosis

It is good practice to confirm a clinical diagnosis if a test is available, although this is not essential if the diagnosis is not in doubt and there are no management implications (eg treatment does not depend on the underlying genetic abnormality, no relatives are requesting carrier screening and parents are not likely to request a prenatal diagnostic test in a subsequent pregnancy). The parents will need to be provided with information about the condition and informed about good sources of further information and support, eg lay support groups. If the condition in question is known to be associated with specific complications, arrangements should be made to screen for these at the appropriate time and a future management plan devised. This will often involve the paediatrician or community paediatrician as the main professional involved in the child's ongoing care and communication between professionals is important. For conditions with a genetic basis, the genetic implications will need to be discussed with the family in a way they can understand and appropriate tests arranged for parents and other relatives. Reproductive options for future preg-nancies should be discussed if appropriate, including options for prenatal testing. Where a condition has a strong environ-mental component e.g diabetic embryo-pathy or fetal alcohol syndrome, the possibilities for prevention or lowering or risk during future pregnancies should be discussed. Parents should be given the opportunity to ask questions and informed how they can make contact if further questions arise.

Summary

The birth of a baby with malformations causes distress for the parents and may also cause a dilemma for the paediatrician, especially when the problems were not suspected during pregnancy or when the diagnosis and prognosis are unknown. Identifying a cause for the malformations, even if they are non easily treatable, can have considerable benefits for the family and guide clinical management. The systematic approach to diagnosis proposed here, together with input from a clinical geneticist will aid diagnosis in many cases.

Acknowledgement

The author would like to acknowledge the support of DYSCERNE: A European Network of Centres of Expertise for Dysmorphology.

References

1. **Winter-Baraitser Dysmorphology Database.** London Medical Databases.® LMD 2006.
2. **Jones K.** Smith's Recognisable Patterns of Human Malformations. Sixth Edition. Saunders. 2005.
3. **Approach to the Child with Dysmorphism or Developmental Delay.** In: Firth H.V., Hurst J.A., Hall J.G., eds. Oxford Desk Reference; Clinical Genetics. Oxford University Press. 2005: 4.
4. **Reardon W.** The Bedside Dysmorphologist. Oxford University Press. 2007.
5. **Hall J., Allanson J., Gripp K., Slavotinek A.** Handbook of Physical Measurements. Oxford University Press. 2006.
6. **Aase J.M.** Diagnostic Dysmorphology. Springer. 1990.