Dysmorphic neonate: an approach to diagnosis in the current era

Vishal Vishnu Tewari1*, Ritu Mehta2 and Kunal Tewari3
1Senior Advisor (Pediatrics and Neonatology), Department of Pediatrics, Army Hospital (Referral and Research), New Delhi, India
2Classified Specialist (Pathology), Oncopathology fellow AIIMS, New Delhi, India
3Classified Specialist (Anaesthesia), Department of Anaesthesia, Base Hospital, New Delhi, India

Abstract
A dysmorphic neonate is a cause of concern and anxiety for the parents and the physician. Making a clinical diagnosis allows a targeted search for a genetic aetiology in order to correctly delineate the healthcare requirements of the infant and also allows the parents to search for and join a ‘support group’. It allows a more accurate estimate of the risk of recurrence and therefore allows genetic counselling. It allows prognostication and permits interventions that may prevent, anticipate or more successfully treat complications. The approach to a dysmorphic neonate is similar to making a diagnosis of a neonate with any systemic illness and relies on a detailed history, a meticulous clinical examination, identifying a syndrome based on a combination of signs, or sometimes ‘by gestalt’. Cytogenetics and molecular techniques improve our ability to make precise syndrome diagnoses. Eventhough there is a certain degree of urgency in making a diagnosis in a dysmorphic neonate, a snap diagnosis should never be made. Around 4,000 malformation syndromes have now been delineated and many are associated with medical problems. Thus making a specific syndrome diagnosis can influence immediate medical management. A detailed history, a physical examination for detailing the major and minor anomalies, recording the growth, examination of previous records and photographs are complemented by cytogenetics and molecular genetic techniques in achieving a diagnosis. Familiarity with dysmorphology databases and cross referencing the anomalies especially the rarer ones helps in narrowing the differential diagnosis.

Introduction
Dysmorphology is a branch of clinical genetics in which clinicians and researchers study and attempt to interpret the patterns of human growth and structural defects. A dysmorphic neonate at birth is a cause of concern and anxiety for the parents and also the physician. If the dysmorphism does not result in a major anomaly and the parents are unaware of the presence of a dysmorphic syndrome in their newborn, breaking the news, bringing the variations to the notice of the parents, characterizing all major and minor anomalies accurately, establishing and confirming the diagnosis and providing genetic counselling are the immediate responsibilities of the physician. Providing health care supervision for the child on follow-up as per the established guidelines is subsequently required and can be done accurately only if the diagnosis is confirmed. With the increasing identification of genetics in the causation of disease, reaching a clinical diagnosis also allows a more targeted search for a genetic aetiology. Making a diagnosis also allows the parents to search for and join a ‘support group’ and interact with other parents with children having the same or similar problems. This helps the parents to cope with stress of having a dysmorphic baby. The approach to making a diagnosis of a dysmorphic neonate is fundamentally similar to making a diagnosis of a neonate with any systemic illness and relies on a detailed history, a meticulous clinical examination, identifying a syndrome based on a combination of signs, or sometimes ‘by gestalt’ (pattern recognition). Cytogenetics and molecular techniques improve our ability to make precise syndrome diagnoses. Even though there is a certain degree of urgency in making a diagnosis in a dysmorphic neonate, a snap diagnosis should never be made, as experience teaches us that in most cases they are wrong and an infant could carry on with a wrong diagnosis for many months before it may get corrected [1].

The basic concepts of dysmorphology
The word ‘dysmorphic’ originates from a greek word ‘dys’ meaning disordered and ‘morph’ meaning shape or form. The term ‘dysmorphology’ was coined by Dr David Smith in 1960’s in USA. Around one in 40 or 2.5% of all newborns have a malformation at birth. 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. Many are associated with medical problems and making a specific syndrome diagnosis can influence immediate medical management. However, the child with dysmorphism often does not have a major malformation, and may simply have an appearance that is unusual compared with the general population and of unaffected close relatives [2]. Most syndromes occur due to one of the following causes:-

a. Single gene disorders e.g. Apert syndrome
b. Chromosomal disorders e.g. Down syndrome
c. Microdeletion syndromes e.g. Prader-Willi syndrome

Correspondence to: Vishal Vishnu Tewari, Senior Advisor (Pediatrics and Neonatology), Department of Pediatrics, Army Hospital (Referral and Research), New Delhi, India, Tel: +91-8826118889, E-mail: docvvt_13@hotmail.com

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d. Polygenic disorders e.g. club foot

e. Environmental causes (Teratogenesis) e.g. Rubella, congenital viral infection, infant of diabetic mother (IDM)

Some inborn errors of metabolism may result in dysmorphism e.g. peroxisomal disorders (Zellweger syndrome), pyruvate dehydrogenase deficiency, glutaric aciduria type II. These are progressive in nature with worsening of the dysmorphism with time [3]. Syndromes due to chromosomal anomalies are non-progressive but the phenotype may become more explicit with time e.g. Smith-Magenis syndrome [1]. A genetic etiology should be suspected if the infant has any of the following: [4]

a. Congenital anomalies: one or more major anomaly or more than two minor anomalies

b. Poor growth: symmetric intrauterine growth restriction or postnatal growth failure

c. Developmental delay or developmental regression

d. Craniofacial dysmorphism

e. Ambiguous genitalia

A basic knowledge of the embryologic and fetal development is integral to understanding of the susceptibility to dysmorphism which is highlighted in the Figure 1 [5]. Critical periods during the development of the fetal organs during which teratogenic influences lead to anomalies and dysmorphism can be understood from Figure 2 [6]. The definition of terms commonly used in description of birth defects is as given below in Table 1 [2,7]. Syndrome diagnosis depends upon good clinical skills, knowledge of the description and definition of human phenotypic variations, experience of the examiner supported by dysmorphology databases and cytogenetics and molecular genetic studies. There is undoubtedly an element of ‘intuition’ which is unteachable and this ability combined with reading and recall results in the ‘edge’ that some clinicians have over others. The definition of common clinical signs seen in dysmorphic syndromes were neatly outlined ironing out ambiguous or unclear references through the efforts of a group of over 30 clinical geneticists from the United States, Canada, Europe, and Australia. These consensus definitions have been published in the ‘American journal of clinical genetics’ in 2008 [8-14]. The reader is encouraged to look at this reference to improve his or her understanding of these signs. A similar but shorter and less exhaustive list is given in Table 2 [7]. It is also useful to categorize abnormalities as ‘major’ or ‘minor’ birth defects. Major anomalies are those that either cause dysfunction (absence of a digit) or require surgical correction (polydactyly), while minor anomalies which occur in less than 5% of the population neither cause significant dysfunction nor require surgical correction (mild cutaneous syndactyly). The significance of identifying the ‘minor’ anomalies is that they herald the increased risk or the

Figure 1. Embryologic and fetal susceptibility to anomalies.

Figure 2. Critical periods during the development of the fetal organs during which teratogenic influences lead to anomalies and dysmorphisms.
The significance of identifying ‘minor’ anomalies

| Minor anomaly                        | Significance                                |
|--------------------------------------|---------------------------------------------|
| Occurrence of a single minor anomaly | 15% of all newborns                         |
|                                      | 3% have an associated major anomaly         |
| Occurrence of two minor anomalies    | Less common 0.8%                            |
|                                      | 11% have an associated major anomaly        |
| Presence of three or more minor      | Unusual 0.5%                                |
| anomalies                            | 90% have an associated major anomaly        |
| External minor anomalies in the head | Constitutes 71% of minor anomalies          |
| and neck region and the hand         |                                             |

The need to ‘know’

Neonates who are noted to be dysmorphic at birth carry a significantly higher risk of a major anomaly and are at a higher risk for having developmental delay. It can be an emotional roller coaster ride for a couple to know that the baby is dysmorphic, yet the diagnosis is not known and there may be a therapeutic intervention albeit rare but not being offered owing to the inability to achieve an accurate diagnosis. Making a clinical diagnosis makes it possible to attempt a targeted genetic diagnosis. It allows a more accurate estimate of the risk of recurrence and therefore allows genetic counselling. It allows prognostication and permits interventions that may prevent, anticipate
or more successfully treat complications. It helps the family reach out to specific support groups and therefore helps in the coping process.

Table 4. Minor anomalies seen in various systems.

| System   | Minor anomaly                                                                 |
|----------|-------------------------------------------------------------------------------|
| Craniofacial |                                                                                   |
|          | Large fontanel                                                                |
|          | Flat or low nasal bridge                                                       |
|          | Saddle nose, upturned nose                                                     |
|          | Mild micrognathia                                                              |
|          | Cutis aplasia of scalp                                                         |
| Eye      | Inner epicanthal folds                                                         |
|          | Telecanthus                                                                   |
|          | Slanting of palpebral fissures                                                  |
|          | Hypertelorism                                                                  |
|          | Brashfield spots                                                               |
| Ear      | Lack of helical fold                                                          |
|          | Posteriorly rotated pinna                                                       |
|          | Preauricular with or without auricular skin tags                               |
|          | Small pinna                                                                   |
|          | Auricular (preauricular) pit or sinus                                          |
|          | Folding of helix                                                               |
|          | Darwinian tubercle                                                             |
|          | Crushed (crinkled) ear                                                          |
|          | Asymmetric ear sizes                                                           |
|          | Low-set ears                                                                  |
| Skin     | Dimpling over bones                                                            |
|          | Capillary hemangioma (face, posterior neck)                                    |
|          | Mongolian spots (African Americans, Asians)                                    |
|          | Sacral dimple                                                                 |
|          | Pigmented nevi                                                                |
|          | Redundant skin                                                                 |
|          | Cutis marmorata                                                                |
| Hand     | Simian creases                                                                 |
|          | Bridged upper palmar creases                                                   |
|          | Clinodactyly of fifth digit                                                    |
|          | Hyperextensibility of thumbs                                                   |
|          | Single flexion crease of fifth digit (hypoplasia of middle phalanx)            |
|          | Partial cutaneous syndactyly                                                   |
|          | Polydactyly                                                                   |
|          | Short, broad thumb                                                             |
|          | Narrow, hyperconvex nails                                                      |
|          | Hypoplastic nails                                                              |
|          | Camptodactyly                                                                 |
|          | Shortened fourth digit                                                         |
| Foot     | Partial syndactyly of second and third toes                                    |
|          | Asymmetric toe length                                                          |
|          | Clinodactyly of second toe                                                     |
|          | Overlapping toes                                                               |
|          | Nail hypoplasia                                                                |
|          | Wide gap between hallux and second toe                                         |
|          | Deep plantar crease between hallux and second toe                              |
| Others   | Mild calcaneovalgus                                                            |
|          | Hydrocele                                                                      |
|          | Shawl scrotum                                                                  |
|          | Hypospadias                                                                    |
|          | Hypoplasia of labia major                                                      |

Approach to a neonate with dysmorphism

The approach to diagnosing a dysmorphic neonate is as follows:

a. History including perinatal details and family history
b. Physical examination detailing the minor and major anomalies
c. Growth recording and measurements
d. Examination of previous records and photographs
e. Making a diagnosis based on the above details:
   i. Ballpark diagnosis: an ‘approximation’ of the diagnosis based upon the clinical features.
   ii. Diagnosis by Gestalt: identifying the syndrome by ‘pattern recognition’.
   iii. Syndrome search: searching a dysmorphology database using the key anomalies noted in the baby
f. Investigations to confirm the diagnosis and to evaluate the neonate for affected organ systems.

History

History of consanguinity suggests the possibility of an autosomal recessive disorder. Male baby with similarly affected male siblings or maternal male relatives suggests X-linked disorder. Vertical transmission suggests an autosomal dominant disorder, especially male to male transmission. History of two similarly affected siblings but of different sexes points to a possible mitochondrial disorder. History of fever with rash and polyarthralgia during pregnancy especially during the first trimester suggests a congenital infection. Drawing a three generation family tree identifies similarly affected family members and also indicates the pattern of mendelian inheritance. Recurrent miscarriages may suggest that parents are carriers of balanced chromosomal rearrangement. The occurrence of more than two first-trimester miscarriages increases the probability of finding a balanced translocation in one parent. History of maternal diabetes mellitus, acute fatty liver of pregnancy and HELLP syndrome seen in mothers carrying a fetus with a fatty acid oxidation defect should be taken. History of maternal exposure to drugs or radiation should be taken. History of alcohol or tobacco use by the mother during pregnancy should be asked. Severe hyperemesis has been linked with dysmorphic facial features and skeletal abnormalities. History of fetal akinesia or hypokinesia should be asked. The antenatal ultrasound should be examined for dating of the pregnancy, fetal growth, fetal lie and skeletal abnormalities. History of fetal akinesia or hypokinesia should be asked. The antenatal ultrasound should be examined for dating of the pregnancy, fetal growth, fetal lie and skeletal abnormalities. Severe hyperemesis has been linked with dysmorphic facial features and skeletal abnormalities. History of fetal akinesia or hypokinesia should be asked. The antenatal ultrasound should be examined for dating of the pregnancy, fetal growth, fetal lie and skeletal abnormalities. Some syndromes are associated specifically with intra-uterine growth retardation and others with fetal overgrowth. Mechanical constraint caused by uterine abnormalities e.g. bicornuate uterus can lead to fetal deformation and explain an unusual head shape or the presence of talipes deformity. Anomaly scans if available add useful information including identification of anatomic variations referred to as soft markers. But a combination of 2 or more soft markers only may indicate an underlying syndrome e.g. nuchal translucency and chordoid plexus cyst. Results of maternal triple screen or amniocentesis/chorionic villus biopsy results if available should always be examined. History of intracytoplasmic fertilization (ICSI) and a large placenta indicates Beckwith–Weidemann syndrome. History of ICSI is also implicated in the causation of uniparental disomy.
Table 5. A list of common dysmorphic syndromes encountered during the neonatal period and the lab test for confirming the diagnosis.

| Condition                  | Presenting feature                               | Diagnostic test                      |
|----------------------------|--------------------------------------------------|--------------------------------------|
| Trisomy 21                 | Brachycephaly, small ears, hypotonia, AVSD, single palmar crease, sandal gap, Hirschsprung disease | Karyotyping                          |
| Down syndrome              |                                                  |                                      |
| Trisomy 18                 | Contracture of fingers, globular head, dysplastic ears, low birth weight, heart defects, short great toes, radial aplasia | Karyotyping                          |
| Edward syndrome            |                                                  |                                      |
| Trisomy 13                 | Holoprosencephaly, cleft, heart defect, polydactyly, renal abnormalities, microphthalmia | Karyotyping                          |
| Pallud syndrome            |                                                  |                                      |
| 4p-Wolf-Hirschorn syndrome | Hypertelorism, prominent glabella (Greek helmet), cleft lip and palate, short philtrum, large ears | May be visible on standard karyotype. More reliably detected by FISH or MLPA |
| 5p-Cri du Chat syndrome    | Mewing cry, microcephaly, round face, prominent epicantus folds, cleft palate, ear anomalies | Usually visible on routine karyotype. FISH will detect smaller deletions. |
| 12p tetrasyndrome          | 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 |
| Pallister Killian syndrome |                                                  |                                      |
| 22q11 deletion             | Cardiac defects especially outflow tract, Cleft palate, micrognathia, prominent nose, overarched heels of ear, hypocalcaemia, absent thumbs | FISH for 22q11 deletion. Few have smaller deletions detectable on MLPA of 22q11 |
| DiGeorge syndrome          |                                                  |                                      |
| Velocardiofacial syndrome  |                                                  |                                      |
| 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  | Examine mother DNA for expansion in myotonic dystrophy gene on chromosome 19 |
| Beckwith-Weidemann 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, esophthalmos, dislocated lenses, wrinkly skin, heart murmur | Cardiac echo and follow-up as aortic dilatation may not be present at birth. Eye examination, FN1 mutation analysis |
| Rubinstein-Taybi syndrome  | Broad mediially 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 Heterogenous 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 1 collagen genes |

15 leading to Angelman syndrome. Therefore, history of the mode of conception – natural or assisted should be taken. Intrauterine growth restriction with discordant fetal growth from early pregnancy suggests the possibility of chromosomal anomalies, congenital malformations or fetal infection, while in-utero fetal growth restriction noted from the third trimester is mostly due to placental dysfunction and would result in an asymmetric IUGR baby. Finally an inquiry into the circumstances at the time of birth, including delayed cry, the need for resuscitation, apgar scores and whether the baby was breast feeding from day one of life should be taken [1,2,7,15,16].

Physical examination detailing the major and minor anomalies

A comprehensive examination detailing the major and minor anomalies must be done. A record of the weight, length, occipito-frontal circumference and ponderal index in IUGR babies at birth should be made. An examination of the dermatoglyphic patterns may occasionally be rewarding e.g. excessive arches are seen in trisomy 13, trisomy 18, Klinefelter syndrome (47XXY), cri-du-chat syndrome (5p-) and fetal phenytoin exposure. Excessive ulnar loops are seen in trisomy 21. Excessive whorls are seen in Turner syndrome (45XO), Smith-Lemli-Opitz syndrome and 18p deletion. Deltas, or triradii, form at the convergence of three sets of ridges on the palm. This junction is where the hypothenar, thenar, and distal palmar patterns converge. There are typically no triradii in the hypothenar area of the palm but when patterning is present or is large, a distal triradii arises, which is found in only 4% of normal individuals but in 85% of babies with trisomy 21. Certain clinical clues can go a long way in helping the clinician make the diagnosis e.g. hypocalcemic seizures with absent thymic shadow and a conotruncal cardiac lesion is seen in DiGeorge syndrome. Hypersensitivity to high pitched sounds, hypocalcaemia, supravalvular aortic stenosis or isolated pulmonary stenosis is seen in William syndrome. A history of developmental delay, temper tantrums, occasional self-injury and sleep disturbances is seen in Smith-Magenis syndrome [1,2,7,15,16].

Growth recording and measurements

Measurements such as height, weight (usually reflecting nutrition), and head circumference should be plotted on neonatal growth charts. Gestational age–appropriate charts should be used for premature infants. It is often helpful to express values that are outside the normal range as 50th percentile for a different gestational age. For example, a full-term baby with microcephaly may have a head circumference of less than the 5th percentile for 38 weeks. This can be expressed as a measurement at the 50th percentile for 33 weeks, which imparts the degree of microcephaly more clearly. Important measurements include...
head circumference, inner and outer canthal distances, interpupillary distances, ear length, ear placement, internipple distances, chest circumference and hand and foot lengths. Other graphs and measurements using age-appropriate standards can be found in compendia such as the Handbook of Physical Measurements [2,17].

Examination of previous records and photographs

An examination of the previous growth records would help in assessing the growth velocity and the pattern of growth. The element of subjectivity in the diagnosis of some syndromes especially at the mild end of a syndrome’s spectrum has resulted in more objective diagnostic approaches such as photogrammetry and anthropometrics. Photogrammetry uses objective measurements from standardized photographs, and anthropometry from standardized physical landmarks, to assess patients objectively [17,18].

Making a diagnosis

Following the history and physical evaluation, the clinician has full details about the neonate including the major and minor anomalies. If the diagnosis is not apparent based upon ‘pattern recognition’ (diagnosis by gestalt based on the examiner’s personal experience and abilities) by now, the clinician can cross reference two or more anomalies in order to create a differential diagnosis and a most-probable diagnosis (the probable diagnosis ‘approximates’ as closely as possible the true diagnosis). Narrowing the possibilities down to a few allows diagnostic testing. If there are multiple anomalies, it is prudent to use the least common ones. Cross referencing is best accomplished by using published compendia of malformation syndromes. These compendia have been supplemented by databases that are accessible online (i.e., GeneReviews, Online Mendelian Inheritance in Man (OMIM), and PubMed) [19-21]. A ‘syndrome search’ can be then conducted on these online databases. The availability of such tools allows the cross referenced features to be compared easily with those of other described syndromes having similar malformations. This systematic review produces a differential diagnosis for the constellation of features described and identifies relevant literature published in this regard.

Use of dysmorphology databases

Databases are now considered indispensable in clinical genetics and dysmorphology. Some resources such as Online Mendelian Inheritance in Man (OMIM) have free access. It is an excellent tool for the identification of key journal references, for summaries of clinical features of classical cases and family studies of Mendelian disorders, and for obtaining an indication of the research progress in terms of new landmark discoveries. The databases include combinations of clinical features such as associated malformations, other syndromes, and syndromic features. The identifications of the microdeletion syndromes e.g. Prader-Willi syndrome, Angelman syndrome, Smith-Magenis syndrome, Miller-Dieker and DiGeorge syndrome. Three techniques of FISH are commonly applied in dysmorphology. First, probes that are specific to the gene locus on the chromosome, bind to the segment of DNA which is not visible by G-banding and are usable by light microscopy. If the gene is deleted the FISH probe will not bind, thus demonstrating the microdeletion. Second, in whole chromosome painting (WCP), FISH probes are specific to a complete individual chromosome, rather than a single locus, and will paint the entire chromosome. Different approaches include combining fluorescent dyes to give each chromosome pair plus the X and Y chromosomes a different colour on a single metaphase spread and examining each chromosome separately, or a restricted set of chromosomes, in individual wells on a single slide. WCP is useful for identifying the origin of additional chromosome material that is microscopically visible but not distinctive enough to be assigned to a specific chromosome. It can also be used to search for large visible chromosome rearrangements in deletion or addition of material. These rearrangements involve an entire arm of a chromosome or may be submicroscopic. Such submicroscopic deletions can often be detected by targetted fluorescence in situ hybridization (FISH) probes specific for the deleted region, allowing the identification of the microdeletion syndromes e.g. Prader-Willi syndrome, Angelman syndrome, Smith-Magenis syndrome, Miller-Dieker and DiGeorge syndrome. Three techniques of FISH are commonly applied in dysmorphology. First, probes that are specific to the gene locus on the chromosome, bind to the segment of DNA which is not visible by G-banding and are usable by light microscopy. If the gene is deleted the FISH probe will not bind, thus demonstrating the microdeletion. Second, in whole chromosome painting (WCP), FISH probes are specific to a complete individual chromosome, rather than a single locus, and will paint the entire chromosome. Different approaches include combining fluorescent dyes to give each chromosome pair plus the X and Y chromosomes a different colour on a single metaphase spread and examining each chromosome separately, or a restricted set of chromosomes, in individual wells on a single slide. WCP is useful for identifying the origin of additional chromosome material that is microscopically visible but not distinctive enough to be assigned to a specific chromosome. It can also be used to search for large visible chromosome rearrangements in deletion or addition of material. These rearrangements involve an entire arm of a chromosome or may be submicroscopic. Such submicroscopic deletions can often be detected by targetted fluorescence in situ hybridization (FISH) probes specific for the deleted region, allowing the identification of the microdeletion syndromes e.g. Prader-Willi syndrome, Angelman syndrome, Smith-Magenis syndrome, Miller-Dieker and DiGeorge syndrome.
breaks and exchanges, and are difficult to visualize on a standard G-banded karyotype. Subtelomeric probes are superior to WCP techniques for uncovering cryptic translocations. Genomic variations which lie between the easily identifiable chromosomal anomalies on the standard karyotype and the single nucleotide polymorphisms (SNP) are identified using DNA microarrays. DNA microarrays detect copy number variations (CNV). Larger chromosomal rearrangements such as balanced translocations or inversions are not detectable using this method. Microarray testing can be performed in either a targeted or genome-wide fashion. Two types of DNA microarray platforms used currently are array comparative genomic hybridization (array CGH) and single nucleotide polymorphism arrays (SNP arrays). Array CGH uses bacterial artificial chromosomes containing large DNA segments as probes, or small oligonucleotides as DNA probes. SNP arrays use probes based on known polymorphisms in the human genome. SNP arrays detect gains or losses of shorter stretches of the genome as the probes for a given region are densely arrayed, and thus the sensitivity for detecting alterations of that region is higher. SNP arrays can detect consanguinity. With a single test, microarrays can detect genomic errors associated with disorders that are usually identified by cytogenetic analysis and multiple FISH studies. Microarray analysis thus provides robust and exceptional level of resolution from a diagnostic perspective. However the interpretation of the results in assigning causality and clinical significance of the multiple alterations that are detected in each individual is not clear. Towards this end, the availability of databases with information on normal variation in multiple ethnic populations and testing of unaffected parents remain standard approaches to discerning whether a CNV is responsible for the dysmorphism or likely to cause disease in the future. Based on current evidence it is recommended that Chromosomal microarray be ordered as the first tier genetic test in place of a karyotype for patients with unexplained multiple congenital anomalies. High detection rates of CNV’s in neonates with birth anomalies has been demonstrated using chromosomal microarray. Molecular testing provides several answers – confirming the diagnosis, the cause of the anomaly, identifying family members at risk. It establishes a diagnosis in a symptomatic individual, identifies the inheritance pattern, and provides carrier testing and prenatal testing. Over 2500 tests are available. Molecular testing may be for a single gene or multi-gene testing. In single gene study sequence analysis for missense, nonsense and splice site mutations is done. Small intragenic deletions/insertions are identified and testing for deletion/duplication of exons or whole gene is also done. In the ‘phenotype first approach’ clinician uses detailed phenotypic features to determine genes most likely to be mutated. In multi-gene panels the clinician identifies a broad phenotype and a panel of genes are then tested. The panel varies depending upon the mutations prevalent in that ethnic or geographic population. Next generation sequencing tests such as the whole genome sequencing (WGS) and the whole exome sequencing (WES) have been introduced to facilitate diagnosis as they can be wrong and induce anxiety in the parents. Be sensitive towards the stress the parents are facing.

Key learning points

1. The diagnosis of a dysmorphic neonate is a systematic exercise, with no recourse other than a meticulous history and a thorough and repeated clinical examination.

2. One must curtail the inherent tendency to make ‘spot’ diagnosis as they can be wrong and induce anxiety in the parents. Be sensitive towards the stress the parents are facing.

3. One must get familiar with the common clinical signs in dysmorphic syndromes and the minor anomalies that occur.

4. Meticulous recording of growth parameters and physical measurements and comparing them with age-appropriate standards as given in the Handbook of Physical measurements, and characterizing all major and minor anomalies is crucial.

5. Familiarity with dysmorphology databases and cross referencing the anomalies especially the rarer ones helps in narrowing the differential diagnosis.

6. Current evidence recommends chromosomal microarray as the first tier investigation in place of karyotyping in neonates with multiple congenital anomalies.

Contribution

Vishal Vishnu Tewari (VVT) and Ritu Mehta (RM) have contributed in conception, designing of data and writing of this article. Kunal Tewari (KT) was responsible for revision of the manuscript for important intellectual content. VVT is responsible for overall supervision and is the guarantor of the article.

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