Approach to Congenital structural anomalies in the newborn

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- Congenital anomalies only implicate presence of morphogenic anomalies in organs/ body parts at birth (often intrauterine) and do not implicate etiology such as genetic/ teratogenic etc
- Global birth prevalence: 2- 3%
- These may be **major**, producing functional impairment and requiring medical/surgical treatment (e.g.,esophageal atresia) or minor which generally do not require treatment (e.g., clinodactyly). **Minor** anomalies are often phenotypic variants commonly seen in the general population (e.g., clinodactyly)
- Congenital anomalies may be **isolated or multiple**: within a system/ in related structures or in different, seemingly unrelated structures, latter mainly due to affection of developmental fields (e.g., VACTERL) or pleotropic effects of the genes involved in the pathogenesis (e.g.,TBX5, Holt-Oram syndrome: cardiac and thumb anomalies). Sometimes multiple anomalies appear following a primary defect such as a spinal open neural tube defect leading to talipes and hydrocephalus.

Table 1: Etiological classification of congenital anomalies

Intrinsic: genetic (chromosomal aberration and gene mutation), or polygenic multifactorial causes explain approximately 45% of all congenital abnormalities while those resulting from the action of an extrinsic factor (teratogenic, nutritional, maternal disorder etc) add up 5% of the congenital anomalies. For the remaining 50% of these abnormalities, the cause may still remain unknown.

Etiology	Example
Chromosomal	Trisomy 18
Microdeletion/duplication syndromes	Di George syndrome (22q11.2 microdeletion)
Single gene defect	Smith Lemli Opitz syndrome with DHCR7 gene mutation
Oligo/polygenic	Holoprosencephaly, cleft palate
Polygenic multifactorial/ eco-genetic	Neural tube defects
Teratogenic • Drugs • Addiction/ abuse • Infection • Maternal disease • Environmental insult • Nutritional	Phenytoin induces NTD, cleft palate Fetal alcohol syndrome Congenital rubella infection Diabetic embryopathy Radiation/ hyperthermia induced microcephaly Folate deficiency leading to NTD, CHD
Others/ miscellaneous	Amniotic band leading to clefting Oligohydramnios or multiple gestation leading to talipes

An apparently isolated anomaly might be caused due to a variety of underlying factors, for example an isolated cleft palate at birth could be polygenic multifactorial, single gene/ chromosomal defect, teratogenic or due to amniotic band syndrome.

Types of congenital anomalies

Malformation: structural/ morphological defects of an organ, or a larger body region resulting from an intrinsically abnormal developmental process, e.g., polydactyly, renal agenesis

Deformation: distortion of a normally developing body part, resulting from mechanical forces, e.g., talipes

Disruption: destruction of a tissue more likely a due to a vascular insult leading to an abnormal form, shape or position of a part of the body which was intrinsically normal, e.g., amniotic band leading to clefting or absent digits of an extremity

A **sequence**is a pattern of multiple defects resulting from a single primary malformation (e.g., CTEV and hydrocephalus resulting secondary to lumbar NTD)

An **association** is a group of malformations occurring together more often than just by chance but without a yet known underlying etiology (e.g., VATER/VACTREL with vertebral, anal, trachea-esophageal, renal and limb abnormalities).

A **syndrome**is a pattern of features often with a unifying underlying cause (e.g., Down syndrome due to trisomy of chromosome 21 or 21q containing the DSCR: Down syndrome critical region)

With improved understanding of molecular basis, an association may get converted into a syndrome: the classical CHARGE association (coloboma of eye, choanal atresia, heart defects, retardation of growth and development, ear defects) is now known to be caused by mutations in CHD7 and SEMA3E genes converting it to CHARGE syndrome.

Commonly associated malformations

It is a dictum to look for additional anomalies if one anomaly is identified. Some anomalies are found to be more commonly associated and they should be specifically looked for when diagnosed pre or postnatally. They may be visible externally or need investigations such as ultrasound, cardiac echo or x-ray, fundoscopy etc.

Some examples are as follows:

- Single umbilical artery (prenatal ultrasound): cardiac, renal
- Cardiac-renal-vertebral-anorectal/esophageal
- Facial-cardiac-hearing-vision
- Renal-genital-spinal

- Limb/ hands-cardiac

Genetic investigations for structural abnormalities

- Documentation of all structural anomalies, associated dysmorphism, growth and developmental anomalies is essential to choose and plan genetic investigations depending on a working etiological diagnosis.
- In utero transfer to a higher medical center with facilities for genetic diagnosis is recommended even if the anomalies are lethal or multiple and non-correctable. This helps in appropriate documentation and sample collection, DNA banking which could help the families in their reproductive planning later.
- Genetic consultation and counseling is a prerequisite to genetic investigations and such tests should be ordered after appropriate counseling and obtaining informed parental consent that discusses use/limitations of the tests.
- Genetic studies need to be deferred for about weeks after blood transfusion (which is a common case in newborns admitted in NICU for a long time). Hence samples should preferably be collected before transfusing blood products. Alternatively, tissue samples such as skin biopsy/ buccal swab may be collected after obtaining parental consent and discussing with the concerned genetics laboratory.
- While certain tests such as karyotyping or chromosome breakage studies (e.g.,in Fanconi anemia) require a fresh blood sample (4-5 cc in sodium heparin collected aseptically), most other genetic studies can be done DNA extracted from blood (4-5 cc EDTA) or tissue (e.g., skin biopsy sample in sterile normal saline or buccal swab).
- American Academy of Medical Genetics has recommended ***chromosomal microarray as a first-tier test for pre/ postnatally diagnosed structural defects***, unless there is an obvious diagnosis such as Down syndrome. Thus, for most multiple structural malformations +/- growth and developmental delay, not typical of a particular syndrome, chromosomal microarray has replaced karyotyping.

- Use of fluorescence in situ hybridization (FISH) is limited to certain chromosomal and microdeletion syndromes for which specific probes are available. A presumptive diagnosis is necessary to order a particular FISH assay, e.g., DiGeorge syndrome (22q11.2microdel) when a cono-truncal cardiac anomaly is associated with absent thymus, hypocalcemia etc or William syndrome (7q11.23 microdel) when aortic stenosis is associated with typical facies and hypercalcemia.
- Single gene sequencing or targeted common mutations can be tested when the diagnosis of a single gene disorder is clinically apparente.g., Achondroplasia. However, in most multiple congenital anomalies that don't fit in any specific syndrome, a combination of microarray and whole exome sequencing is often considered.
- Many couples are financially and emotionally not prepared for genetic studies while their newborns are critical. DNA banking is strongly recommended in such situation which provides an opportunity for genetic studies at a later date irrespective of the outcome, to help in the couple's future reproductive decisions.

Table 2: Genetic tests for congenital anomalies

Test	Specifics	Sample required	Approximate reporting time
Karyotype	Microscopically visible structural and numerical chromosomal aberrations, mosaicism	3-5 cc Blood in sodium heparin or tissue in normal saline collected and transported aseptically	10-14 days
Chromosome breakage studies	Using mitomycin or irradiation	3-5 cc Blood in sodium heparin or tissue in normal saline	10-14 days
FISH	For known numerical anomalies e.g., Trisomy 21 Down syndrome or microdeletion syndromes e.g., DiGeorge syndrome	3-5 cc Blood in sodium heparin or tissue in normal saline	2-14 days, latter in case of metaphase FISH

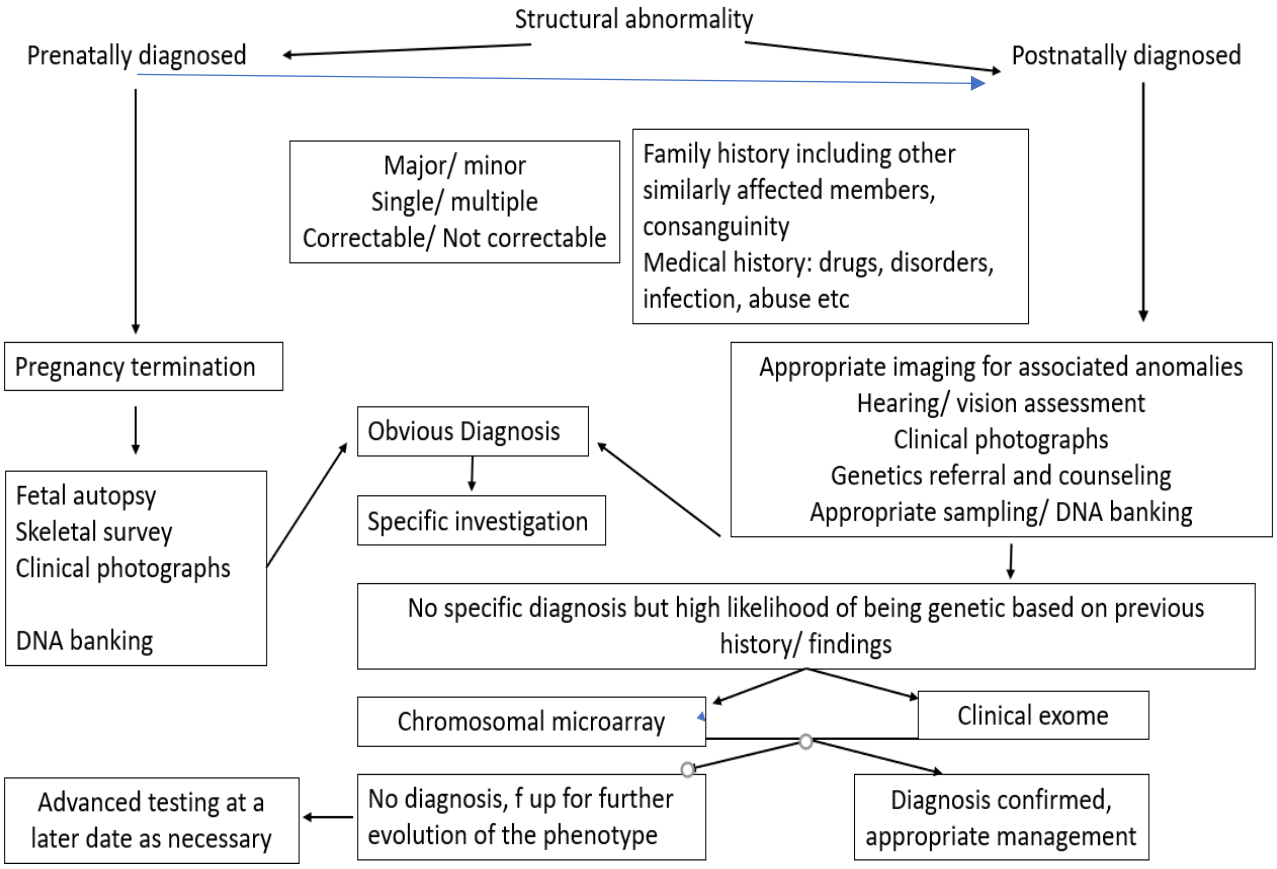
Chromosomal microarray	Microdeletions and duplications	DNA	1-2 weeks
Single gene sequencing	Specific genetic diagnosis should be suspected	DNA	2-8 weeks
Clinical/ whole exome sequencing	Covers exons of selected genes causing genetic syndromes	DNA	4-6 weeks

- **Recurrence risk for congenital structural malformations**
- Families experience emotional-physical-monetary and social burdens when challenged with offspring with congenital anomalies and dealing with pregnancy termination or complicated postnatal period with intensive medical/ surgical management.
- Identifying exact etiology helps such families to answer some of their questions as to "why did it happen" and "whether it will happen again" (recurrence risk to sibs and later offspring of the proband). It serves as the basis of their reproductive decision making and choosing prenatal diagnostic options.
- For most polygenic multifactorial disorders,the recurrence risk to sibs is low 1-3 % if the proband is an isolated case in the family. This risk doubles if there are two sibs similarly affected and increases further with the number of affected individuals in the family.
- For chromosomal and genetic disorders, the recurrence risk depends on whether the abnormality in the offspring is inherited or de novo. In de novo/ spontaneous cases, the recurrence risk is low but germline mosaicism needs to considered. In inherited single gene disorders, the recurrence risk depends on the inheritance pattern such as 25% recurrence risk for autosomal recessive disorder when both parents are carriers of the genetic mutation or 50% risk if one of the parents is affected with the said genetic disorder. Inherited chromosomal aberration when one of the parents is affected or is a balanced carrier, present variable recurrence risks depending on whether mom/ dad is the carrier and which chromosomes are involved etc. For example, an individual

affected with 22q11.2 microdeletion syndrome carries 50% risk of having an affected offspring in each pregnancy while a balanced carrier of Robertsonian t(21;21) carries 100% risk of having an offspring with Down syndrome.

- It is important to emphasize that while periconceptional folate/ multivitamin supplementation helps in reducing some congenital structural defects, not all anomalies can be prevented and baseline population risk of 2-5% of some structural/ functional anomaly in the offspring may exist in any pregnancy.

Fig 1: Approach to congenital anomalies in newborn



Further reading

1. Kenneth Jones, Marilyn Jones and Miguel del Campo Smith's Recognizable Patterns of Human Malformation, 8th Edition, Elsevier publications, 2021

2. Angus Clarke. Harper's Practical Genetic Counselling, Eighth Edition, Taylor & Francis Publishers, 2019