International Journal of Oral & Maxillofacial Pathology. 2013;4(1):15-25
Available online at http://www.journalgateway.com or www.ijomp.org
ISSN 2231 – 2250

Review Article

Oro-Facial Syndromes: An Approach Towards Etiopathogenesis, Diagnosis and Management – A Systematic Review

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Abstract

Currently, there are more than 4,000 genetic disorders identified till date, of which orofacial syndromes form a considerable part. Genetic factors either in isolation or in combination with various environmental factors plays role in causation of these craniofacial anomalies. It becomes a challenge for a dental practitioner to diagnose and manage orofacial syndromes due to their complexity of multisystem involvement. To simplify it classification of orofacial syndromes based on oral manifestations have been suggested. Further, step by step approach of establishing diagnosis including various prenatal and postnatal methods in light of their advantages and disadvantages has been discussed in the present paper. Number of syndromes has been reported till date, unfortunately scientists and doctors are unable to deduce ways to treat most of these. However, the role of symptomatic multidisciplinary management, advanced gene therapy and psychological support to the family members is indispensible. Considering these important areas, attempt has been made through this paper to comprehensively review the aetiology, classification, diagnosis, and management of orofacial syndromes for their better understanding.

Keywords: Pathologic Processes; Diseases; Syndrome; Symptom Cluster; Anomaly; Genetic; Disorders; Chromosome; Genes.

Shally Khanna, Narendra Nath Singh, Vera R Brave, Gadiputi Sreedhar, Anupam Purwar, Shalini Gupta. Oro-Facial Syndromes: An Approach towards Etiopathogenesis, Diagnosis and Management – A Systematic Review. International Journal of Oral & Maxillofacial Pathology; 2013:4(1):15-25. ©International Journal of Oral and Maxillofacial Pathology. Published by Publishing Division, Celesta Software Private Limited. All Rights Reserved.

Received on: 01/10/2012 Accepted on: 16/03/2013

Introduction

In medicine, the term syndrome refers to a combination of symptoms that either result from a single cause or occur together so commonly that they constitute a distinct clinical picture.[1]The heritage of the term syndrome is ancient and derived from the Greek word sundrome: sun, syn – together + dromos, a running i.e., "run together", as the features do.[2]

Human development and its pathological aspects have fascinated mankind since time immemorial. But, inspite of recent great strides in the biological sciences, many aspects of the developmental process remain largely a mystery. The timing of developmental disturbances, types of defects produced, and their modes of inheritance are often complex and poorly understood. Fortunately, many developmental disorders in humans are uncommon, although several hundred different types have now been recognized. More than 300 entities are known to involve the craniofacial structures many including dental tissues. So, genetic factors either in isolation or in conjunction with various environmental factors plays role in causation of these craniofacial anomalies.[3]

A keen observer should look for anything that is away from normal. The fact that a disorder is rare provides no consolation to its victim and dental practitioners have unique role to play in detecting these craniofacial disorders.[3] With this thought for better understanding of craniofacial anomalies or orofacial syndromes, systematic and comprehensive review has been done in the present paper focussing their varied etiology, classification, prenatal and postnatal diagnostic steps, and multidisciplinary management.

Etiopathogenesis

At one time, it was believed that the presence of visible, external malformation was divine punishment for wickedness, occasionally jeopardizing mother's life. Although we have a different understanding of malformations today, the exact cause remains unknown in at least half of the cases[4]. The interaction between genetics and environment is essential especially during early developmental stages. Any disturbance or alteration in these genetic

and environmental factors may lead to various morphological and functional errors and hence to syndromes.

A. Genetic Causes

Changes in DNA due to mutation can cause errors in protein sequence, creating partially or completely non-functional proteins, resulting into a genetic disorder. Many syndromes are due to a genetic anomaly, including chromosomal anomalies, monogenic diseases and metabolic diseases.[5]

1. Chromosomal anomalies

(a) Numerical chromosomal anomalies / aneuploidies: Aneuploid cells have an abnormal number of chromosomes caused by non disjunction during cell division, and disrupting the existing equilibrium in cells. It is of three types, namely Monosomy (2n-1), Nullisomy (2n-2) & Trisomy (2n+1) (Table 1). In humans, the most common aneuploidies are trisomies, which represent about 0.3% of all live births. The numerical chromosomal anomalies are not hereditary in the sense of transmission to the progeny, but still they are anomalies of our hereditary material.[6-11]

Syndrome	Aneuploidy
Turner syndrome	Monosomy X(X0): A female missing an X chromosome
Down syndrome	Trisomy 21: presence of an extra chromosome 21
Patau syndrome	Trisomy 13: presence of an extra chromosome 13
Edwards syndrome	Trisomy 18: presence of an extra chromosome 18
Klinefelter syndrome	XXY: A male who has an extra X chromosome

Table 1: Syndromes associated with aneuploidy

(b) Structural chromosomal anomalies: Results from breakage, followed by loss or rearrangement of genetic material, occurring spontaneously or by exposure to environmental mutagens and are transmissible to the progeny. There exists a large number of structural chromosomal anomalies.[7-11]

(I) Deletion: Refers to loss of a portion of a chromosome. Affected persons nearly always show serious mental handicap and different physical anomalies. E.g. Cri Du Chat Syndrome (5p): part of chromosome 5 is missing; Wolf Hirshorn Syndrome (4p): part of chromosome 4 is missing.

(II) Insertion: When there is a piece of chromosome too much.

(III) Inversion: When part of a chromosome turns 180° around its centre. It is symptomless, unless one of the breakpoints of the inversion disrupts an important gene.

(IV)Translocation: When part of one chromosome become attached to another chromosome.

Structural chromosome anomalies only cause a syndrome when there is an abnormal amount of part of a chromosome: which is sometimes referred to as unbalanced chromosomes, and it can be a partial trisomy or a partial monosomy.[7-11]

2. Single gene abnormalities / monogenic diseases

Single gene disorders are caused by mutations to the DNA sequence in one gene thus disrupts the resulting protein and its function. It is estimated that a single gene disorder occurs in 1 of every 200 births. They are inherited in recognizable, predictable patterns: autosomal dominant, autosomal recessive, and sex-linked[7-11] (Table 2).

Syndrome	Inheritance	Gene Responsible
Apert Syndrome	Autosomal dominant	FGFR2
Meckel Syndrome	Autosomal recessive	MKS1 & MKS2
Robert's Syndrome	Autosomal recessive	ESCO2
VanDer Woude Syndrome	Autosomal dominant	IRF-6

Table 2: Syndromes associated with single gene abnormalities

3. Metabolic disorder

Metabolic disorders are hereditary diseases of the metabolism. They arise by gene mutations, which lead to a deficiency of a particular enzyme, leading to an abnormal metabolism of specific metabolites. Metabolic diseases have a recessive inheritance (autosomal recessive or X-linked recessive).[12]

B. Environmental Causes

Environmental factors are those determinants of disease that are not transmitted genetically and determine the development of disease in those genetically predisposed to a particular condition.[12] In terms of syndromes, commonest environmental cause is teratogenic exposure.

Teratogenic exposure: A teratogen is any chemical, substance, or exposure that may cause birth defects to the developing fetus. The effect of teratogen depends upon the threshold dose and timing of exposure. Exposure during two weeks following conception is unlikely to cause birth defects. Although teratogens may increase the risk for birth defects, they do not necessarily cause problems in all cases. Some common teratogens are listed in Table 3.[8,13]

	Teratogen	Abnormality Produced
Infections	Cytomegalovirus	Hearing loss, microcephaly, mental retardation, visual defects & dental anomalies.
	Rubella	Eye defects, hearing loss, heart defects, mental retardation, & growth retardation.
	Syphilis	Anemia, jaundice, skin rash, mental retardation, growth retardation & dental anomalies.
	Varicella	Congenital varicella syndrome: smaller head, seizures, blindness, mental retardation & intercranial calcifications.
Chemicals, Drugs & Medications	Alcohol	Fetal alcohol syndrome: growth retardation, mental retardation, small head, flat facial profile thin upper lip.
	Thalidomide	Limb defects
	Cigarette smoking	Low birth weights & premature babies.
	Anticonvulsants	Fetal anticonvulsant syndrome: growth and mental retardation, digit hypoplasia and a characteristic face.
Physical Agents	Diagnostic X-rays	Generally do not cause birth defects
	Radiation therapy for cancer	Miscarriage early in preganancy
Maternal Factors	Maternal diabetes	Cardiac defects, spine & limb abnormalities.
	Maternal phenyl ketonuria	Small head size, mental retardation.

Table 3: Teratogens and abnormality produced

C. **Multifactorial**

Multifactorial diseases results by an interaction of genetic and environmental factors. They are more frequent than chromosomal anomalies or monogenic diseases, where each has a frequency of approximately 1%. Congenital multifactorial disorders, including defects such as neural tube defects (spina bifida) or cleft lip/palate affects approximately 3% of the babies. Multifactorial disorders, which manifest themselves on a later age, are much more frequent, such as diabetes, hypertension, or cardiovascular disease. For most of the multifactorial disorders it is still unknown which genes and/or environmental factors play a role. Also the inheritance is frequently unclear. Much is not yet known concerning the environmental factors, which contribute to multifactorial syndromes.[12]

Classification

Various classification systems have been suggested in literature such as etiologic classification, embryonic/histologic classification, monothetic classification, polythetic classification, based on system involvement.[14,15] However, from diagnostic perspective it is important to study orofacial syndromes in association with oral manifestations. Hence, we propose the classification system based on oral manifestations (Table 4 & 5).

Establishing Diagnosis

The first historical evidence of medical syndrome goes back to the 11th Egyptian dynasty[16], and since then it has been a challenging task for any medical practitioner to arrive at conclusive diagnosis of syndrome. The diagnostic steps for syndromes or birth defects can be categorised into prenatal and post natal diagnosis.

PRENATAL DIAGNOSIS

Prenatal diagnosis comprises diagnostic modalities aimed at gaining information about the embryo or foetus in order of ruling in or out foetal anomalies or genetic disorders.[17,18] Methods for prenatal diagnosis can be non-invasive, less invasive and invasive.

A. Non Invasive Methods

1. Preimplantation Diagnosis: It is a procedure in which individuals undergoing in-vitro fertilization have their developing embryos tested genetically prior to implantation in mother's uterus. Polar body and blastomere testing are the two primary methods. In polar body testing, positive test results in two polar bodies ensure that the egg itself is unaffected –therefore, the

mutation has segregated to the polar body, not to the developing ovum. Once an egg is found to be unaffected, it is fertilized via traditional in vitro fertilization and implanted into the uterus. Blastomere method first requires traditional in vitro fertilization, after which cells are grown to the 8-cell stage. One or two cells are harvested and analysed, and an unaffected blastocyst is implanted into the uterus. Preimplantation genetic diagnosis has been successfully performed in cases of Down syndrome, Marfan syndrome and Di-George syndrome.[17-25]

Syndromes of Hard Tissues

Jaws	Agnathia / Micrognathia	Aarskog syndrome, Achondrogenesis, Apert syndrome, Bloom syndrome, Carpenter syndrome, Cerebrocostomandibular syndrome, Cerebro oculo facial skeletal syndrome, Cleidocranial dysplasia, Cohen syndrome, Cowden syndrome, Crouzon syndrome, Goldenhar syndrome, Hallermann streiff syndrome, Marden Walker syndrome, Marfan syndrome, Marshall Smith syndrome, Median cleft face syndrome, Miller syndrome, Multiple pterygium syndrome, Nager syndrome, Noonan syndrome, Orofacial digital syndrome-type2, Pfieffer syndrome, Pierre Robin syndrome, Schwartz Jample syndrome, SHORT syndrome, Stickler syndrome, Treacher Collins syndrome, Turner syndrome, Weaver syndrome.
	Macrognathia	Craniometaphyseal dysplasia, Goltz syndrome, Gorlin syndrome, Mc Cune Albright syndrome, Van Buchem syndrome
	Syngnathia	Popliteal pterygium syndrome, Vander Woude syndrome
Facial Bones	Mid face hypoplasia	Aarskog syndrome, Apert syndrome, Carpenter syndrome, Crouzon syndrome, Nager syndrome, Orofacial digital syndrome, Pfieffer syndrome, Rieger syndrome, SHORT syndrome, Stickler syndrome, Treacher Collins syndrome
	Hemifacial hypoplasia	Goldenhar syndrome, Horner syndrome, Parry-Romberg syndrome
Skull	Microcephaly	Cerebrocostomandibular syndrome, Cerebro oculo facial skeletal Syndrome, Coffin Lowry syndrome, Cohen syndrome, Cornelia de Lange syndrome, Hallermann Strieff syndrome, Lenz microphthalmia syndrome, Marden Walker syndrome, Miller syndrome, Rubinstein Taybi syndrome, Smith Lemli Opitz syndrome
	Macrocephaly	Bardet Biedl syndrome, Cowden syndrome, Gorlin syndrome, Median cleft face syndrome, Maroteaux Lamy syndrome, Marshall Smith syndrome, Van Buchem syndrome, Weaver syndrome
	Brachycephaly	Bardet biedl syndrome, Carpenter syndrome, CHIME syndrome, Cleidocranial dysplasia
Teeth	Hypodontia / Anodontia	Bardet Biedl syndrome, Crouzon syndrome, Down syndrome, Ectrodactyly ectodermal dysplasia, cleft syndrome, Ellis van Creveland syndrome, Ehler Danlos syndrome, Goldenhar syndrome, Goltz syndrome, Gorlin syndrome, Hallermann Strieff syndrome, Hypohydrotic ectodermal dysplasia, Johanson Blizzard syndrome, Kallmann syndrome, Lenz microphthalmia syndrome, Maroteaux Lamy syndrome, Orofacialdigital syndrome type 2, Popliteal pterygium syndrome, Rieger syndrome, SHORT syndrome, Sturge Weber syndrome, Turner syndrome, Vander Woude syndrome, Williams syndrome, Witkop syndrome
	Hyperdontia	Apert syndrome, Cleidocranial dysplasia, Craniometaphyseal dysplasia, Crouzon syndrome, Down syndrome, Ehler Danlos syndrome, Gardner syndrome, Hallermann Strieff syndrome, Klippel Trenaunay syndrome, Sturge Weber syndrome,
	Microdontia	Blepharocheilodontic syndrome, Cleidocranial dysplasia, Crouzon syndrome, Goltz syndrome, Johanson Blizzard syndrome, Median cleft face syndrome, Rieger syndrome, SHORT syndrome
	Macrodontia	Crouzon syndrome
	Enamel hypoplasia	Goltz syndrome, Hallermann Strieff syndrome, Median cleft face syndrome, SHORT syndrome, Trichodento-osseous syndrome, Williams syndrome
	Dentinal defects	Ehler Danlos syndrome, Osteogenesis imperfect
	Impacted / Unerupted teeth	Aarskog syndrome, Cleidocranial dysplasia, Down syndrome, Gardner syndrome, Maroteaux Lamy syndrome, Noonan syndrome.

Table 4: Syndromes of hard tissues

2. Ultrasonography: Ultrasonography is an ultrasound-based diagnostic imaging technique used to visualize subcutaneous body structures and is usually done at about 9 to 13 weeks of pregnancy. Ultrasonography can be performed either trans-abdominally or trans-cervically. It identifies major foetal structural anomalies and foetal anatomical markers, either of which may be associated with underlying chromosomal disorders, single gene disorders or normal variation, but does not identify the underlying cause. Hence, further tests, amniocentesis or chorionic villus sampling are recommended to identify the cause. [17,26-29]

Syndromes of Soft Tissues

Tongue	Microglossia	Freeman Sheldon syndrome, Goldenhar syndrome, Goltz syndrome.
	Macroglossia	Beckwith Wiedemann syndrome, Down syndrome Hurler syndrome, Maroteaux Lamy syndrome, Multiple endocrine neoplasia syndrome, Stickler syndrome, Sturge Weber syndrome.
	Ankyloglossia	Orofacial digital syndrome type 2, Vander Woude syndrome.
Lips	Microstomia	Freeman Sheldon syndrome, Hallermann Strieff syndrome, Rubinstein Taybi syndrome, Schwartz Jample syndrome.
	Macrostomia	CHIME syndrome, Coffin Lowry syndrome, Fryns syndrome, Goldenhar syndrome, Maroteaux Lamy syndrome.
	Lip pits	Poplieal pterygium syndrome, Sturge Weber syndrome, Vander Woude syndrome.
	Double lip	Ascher syndrome, Peters Plus syndrome
Oral mucosa		Ascher syndrome, Behcet's syndrome, Bloom syndrome, Burning mouth syndrome, Chediak Higashi syndrome, Cowden syndrome, CREST syndrome, Ehler Danlos syndrome, Goltz syndrome, Maroteaux Lamy syndrome, Multiple endocrine neoplasia syndrome, Osler Rendu Weber syndrome, Pachyonchia congenital, Peutz Jeghers syndrome, Plummer Vinson syndrome, Reiter's syndrome, Steven Johnson syndrome, Sturge Weber syndrome, Tuberous sclerosis
Gingiva / Periodontium		Chediak Higashi syndrome, Maroteaux Lamy syndrome, Papillon Lefevre syndrome, Ramon syndrome, Trichodento osseous syndrome
Salivary gland		Sjogren syndrome
Orofacial Clefting		Achondrogenesis, Apert syndrome, Beckwith wiedemann syndrome, Blepharocheilodontic syndrome, Branchio-oculofacial syndrome, Cerebrocostomandibular syndrome, CHIME syndrome, Cornelia de Lange syndrome, Cowden syndrome, Craniofrontonasal syndrome, Crouzon syndrome, Ectrodactyly ectodermal dysplasia, cleft syndrome, Fraser syndrome, Fryns syndrome, Goldenhar syndrome, Goltz syndrome, Gorlin syndrome, Kallmann syndrome, Larsen syndrome, Marden Walker syndrome, Meckel syndrome, Median cleft face syndrome, Michels syndrome, Miller syndrome, Multiple pterygium syndrome, Nager syndrome, Opitz oculo genitor laryngeal syndrome, Orofacial digital syndrome type 1, Orofacial digital syndrome type 2, Peters Plus syndrome, Pierre Robin syndrome, Popliteal pterygium syndrome, Schimmelpenning syndrome, Smith Lemli Opitz syndrome, Stickler syndrome, Treacher Collins syndrome, Vander Woude syndrome, Velocardiofacial syndrome,
Neural defect		Bell's palsy, Craniometaphyseal dysplasia, Eagle syndrome, Glossopharyngeal neuralgia, Melkersson Rosenthal syndrome, Myofacial pain dysfunction syndrome, Mobius syndrome, Ramsay Hunt syndrome, Trigeminal neuralgia, Trotter syndrome, Van Buchem syndrome, Wallenberg syndrome, Winking jaw syndrome,

Table 5: Syndromes of soft tissues

B. Less Invasive Method like Maternal Serum Screening: This test samples the mother's blood between 15 and 18 weeks of gestation for the level of alpha fetoprotein (AFP), human chorionic gonadotrophin (HCG), and unconjugated oestriol (UE_3) (Triplet test); which are of foetal origin and mirror the level of these in foetus. The test identifies risk of trisomy 18, 13 and 21 or an open neural tube defect. Inhibin A assessment, when added to the triple test, yields the so-called quadruple test. Accurate assessment of gestational age is essential for interpreting the biochemical parameters. Thus, recently the measurement of HCG and pregnancy-associated plasma protein A (PAPP-A) in maternal serum between the 11^{th} and 14^{th} weeks of pregnancy have

become increasingly established in combination with nuchal translucency measurement and maternal age.[17,18,30]

C. Invasive Methods

1. Chorionic Villus Sampling: Involves sampling and culturing of chorionic villi (ideally 10 to 20 mg), which are tiny projections that make up part of the placenta. Provides information about foetal genetic and chromosomal status (via karyotyping and in situ hybridization), and is done between 10 to 12 weeks gestation, thus providing earlier and more than 99% accurate results. It can be done either transcervically or transabdominally, using ultrasonography guidance. Rarely, subsequent amniocentesis is required to obtain additional information.[7,8,17,18,30]

2. Amniocentesis: It is one of the most common procedures for detecting abnormalities before birth. It is typically performed at 15 weeks of pregnancy or later. It is done trans-abdominally, using ultrasonography guidance, to withdraw amniotic fluid (15 to 20 ml) containing cells shed by the foetus. Fluid may be cultured and analyzed for foetal genetic makeup. It also enables to measure the alpha-fetoprotein level in the amniotic fluid, more reliably to study neural tube and abdominal wall defects.[7,8,17,18,30]

3. Percutaneous Umblical Blood Sampling (PUBS): It is used when rapid chromosome analysis is needed, particularly toward the end of pregnancy, when ultrasonography has detected abnormality in the foetus pointing to a chromosomal abnormality. However, usually it is performed after 19 to 20 weeks of gestation. Foetal blood sample is obtained by percutaneous puncture of the umbilical cord vein (funipuncture) via ultrasound guidance. Often, results can be available within three to five days.[8,17,18]

4. Fetoscopy: It is an endoscopic procedure performed transabdominally during or after the 18th week of pregnancy, allow access to the foetus, the amniotic cavity, the umbilical cord, and the foetal side of the placenta. It is used to evaluate the foetus for birth defects, such as spina bifida, and collection of blood sample from the umblical cord, which is then analyzed in the laboratory for genetic or chromosomal disorders.[8,29,31] Tests performed in different trimesters of pregnancy have been listed in Table 6, 7 and 8.

Genetic Testing of Sample Obtained

In order to detect the underlying gene or chromosomal defect in genetic disorders, various cytogenetic and molecular cytogenetic techniques are available.

A. Cytogenetics: Cytogenetics is the study of normal and abnormal chromosome structure, describing the relationships between chromosome structure and phenotype, and seeking out the causes of chromosomal abnormalities. Method can determine the nature of the chromosomal defect - aneuploidy, a mosaic, a translocation, a deletion, or an insertion in one or both of the parents, or in the foetus.

1.Karyotyping: Metaphase chromosomes are banded using trypsin followed by Giemsa (light and dark bands), and then analysed under microscope. Cells from bone marrow, blood, amniotic fluid, cord blood, tumor, and tissues including skin, umbilical cord, liver, and many other organs can be used to study. Karyotyping had successfully discovered various numerical abnormalities, e.g. Down syndrome – Trisomy 21, Turner syndrome – Monosomy, X0 condition in females, etc. With the advent of banding techniques that differentially stain chromosomes, i.e., Q, R, C, NOR, and high resolution banding, one can successfully differentiate deletions and translocations within the chromosomes, that would otherwise usually not be seen with conventional banding. Eg. Di-George syndrome and Prader-Willi syndrome.[7,8,17,18,30,32]

2.Fluorescent in Situ Hybridization (FISH): Refers to use of fluorescently labelled probe to hybridize to cytogenetic cell preparations, for the characterization of chromosomal rearrangements and marker chromosomes, detection of micro-deletions, and common aneuploidies. FISH can also be performed on bone marrow smears, blood smears, paraffin embedded tissue preparations, uncultured bone marrow and uncultured amniocytes. For congenital problems usually 20 metaphase cells are scored under fluorescent microscope after hybridization. More than thirty microdeletion syndromes have been described in past two decades using FISH analysis. E.g. Sotos syndrome, 5q deletion, Neurofibromatosis Type 1, 17q11.2 deletion, etc.

New FISH techniques such as comparative genomic hybridization (CGH), spectral karyotyping (SKY), color banding, multiple color FISH (M-FISH), can be used to study structural abnormalities in conjunction with G-banding analysis. FISH with multiple subtelomeric probes can be used to detect subtelomeric aberrations in patients with unexplained mental and developmental disabilities. Interphase FISH can be used for prenatal diagnosis of common aneuploidies of chromosomes 13, 18, 21, X, and Y.[7,8,17,18,30,32]

Test	Sample	Diagnosis
ELISA, Western Blot, PCR	Mother's blood	Aquired immune deficiency syndrome
Ultrasonography	-	Structural abnormalities like hydrocephalus, anencephaly, myelomeningocoele, achondroplasia, spina bifida, duodenal atresia, etc. Absence of fetal nasal bone, increased fetal nuchal translucency are now in common use to detect trisomy 21, trisomy 18, trisomy 13, and turner syndrome. Also used to diagnose Apert syndrome, velocardiofacial syndrome, Di George syndrome, Johanson Blizzard syndrome, Klippel Trenaunay syndrome, Noonan syndrome, multiple pterygium syndrome and popliteal pterygium syndrome.
Targeted ultrasonography	-	Can detect facial cleft, cleft lips/ palate, micrognathia, and congenital cardiac abnormalities.
Chorionc Villus Sampling (CVS)	Mother (cells from placenta)	Genetic testing detect chromosomal disorders in fetus.

Table 6: First Trimester Tests

Test	Sample	Diagnosis
Quadruple screen -Alpha Fetoprotein (AFP) -Unconjugated estriol (UE_3) -Human chorionic gonadotropin (HCG) -Analyte inhibin (Inh)	Mother's blood	Low serum AFP, low UE_3 and elevated HCG is indicative of Down syndrome, whereas low levels of all three suggest trisomy 18.
Alpha Fetoprotein (AFP) ELISA Test	Mother's blood	Expanded AFP level may indicate an increased risk of having neural tube defects such as anencephaly, spina bifida and birth defect of the abdominal wall.
Amniocentesis	Mother (Amniotic fluid)	Genetic testing detects chromosomal abnormalities such as related to 13, 18, 21, X and Y chromosomes. High level of AFP level in amniotic fluid is indicative of neural tube and abdominal wall defect.
Percutaneous Umblical Blood Sampling (PUBS)	Fetal blood sample obtained from vein in the umbilical cord	Genetic testing detect chromosomal abnormalities
Fetoscopy	-	Evaluate the foetus for birth defects, such as spina bifida
Ultrasonography	-	As above

Table 7: Second Trimester Tests

Test	Sample	Diagnosis
Amniocentesis	As above	As above
Percutaneous Umblical Blood Sampling	As above	As above

Table 8: Third Trimester Tests

B. Molecular Cytogenetics: Molecular cytogenetics is the study of single gene disorders using new technologies that combine cytogenetic and molecular techniques. Choosing which technique to use depends upon the suspected disorder.

1. Direct DNA Analysis: Analyse a target segment of DNA for the presence of a

specific mutation. It requires knowledge of the correct sequence for the specific gene or DNA segment before analysis. Once known, the sample sequence may be compared to the known, 'model'. This can be accomplished by various methods, namely mutation analysis with restriction enzymes; sequencing of restriction enzyme products; and dot blot.[18,32]

2. Linkage analysis: This aims to find out the rough location of the defected gene relative to another DNA sequence called a genetic marker, which has its position already known. In case of disease gene, the alternative alleles will be the normal allele and the disease allele can be distinguished by looking for occurrences of the disease in a family tree or pedigree. Disease genes are mapped by measuring recombination against a panel of different markers spread over the entire genome. If recombination occur, this indicates that the disease gene and marker are far apart. Some markers however, due to their proximity, will not recombine with the disease gene and these are said to be linked to it. Ideally, close markers are identified that flank the disease gene and define a candidate region of the genome between 1 and 5 million bp in length. The gene responsible for the disease lies somewhere in this region.[18,32]

POST NATAL DIAGNOSIS

Postnatal is the period beginning immediately after the birth of a child. Primary method of establishing postnatal diagnosis of syndromes of head and neck is by means of their clinical signs and symptoms. Hence participation of a dentist plays very important role. Here comes the implication of classification of orofacial syndromes based on oral manifestations, already mentioned by inclusion and exclusion of clinical oral manifestations, look for concurrence of features and suspected syndrome. Further, the diagnosis can be confirmed by, other methods like craniofacial anthropometry, radioimaging, biochemical tests, and genetic tests depending upon the suspected syndrome (Table 9).[17,18,32-35]

Test	Purpose	Example
Craniofacial anthropometry	Growth related abnormalities	Ear length is important in the evaluation of congenital anomaly syndrome such as Down's syndrome. Williams syndrome is characterized by a long philtrum. Di George and Cohen syndromes have short philtrum. Wide mouth is found in Goldenhar syndrome. Short mouth accompanies Craniocarpotarsal Dysplasia.
Radioimaging	Skeletal and dental malformations	OPG, specialized radiographs, CT scan and MRI scan to rule out abnormalities of cranium, jaws, facial bones and teeth.
Biochemical tests (Enzyme and Hormonal assessment)	Metabolic alterations	Plasma insulin test for hyperinsulinism in Beckwith Wiedemann syndrome and Sotos syndrome. α-L-iduronidase deficiency test for Hurler syndrome and Scheie syndrome. N-Acetylgalactosamine 4-sulfatase deficiency test for Maoteaux Lamy syndrome Heparan N-sulfatase, α-N-Acetylglucosaminidase, Acetyl-CoA: α-glucosaminide acetyl transferase, N-Acetylglucosamine-6-sulfatase deficiency tests for Sanfilippo syndrome. β-Glucuronidase deficiency tests for Sly syndrome
Genetic tests	Genetic abnormalities	Karyotyping, FISH, Direct DNA/Mutation analysis, and Linkage analysis

Table 9: Postnatal Diagnostic Tests

Pitfalls in Diagnosis

Correlation of phenotypic alterations with the underlying genetic or environmental causative factors is exhaustive. Due to features like obesity, hypertension, cardiac disease, respiratory disease, diabetes, and depression which are common in general non syndromic population, it becomes difficult sometimes to decide on who should be screened for the possibility of syndrome. Each step in diagnosis has got limitations, for which a clinician should be aware of so as to avoid any misdiagnosis and hence, wrong treatment (Table 10).[8,17,18,23,29,31]

Management

Prevention is always better than cure. This could be implicated for syndromes with known aetiology and features. Especially the genetic ones, that can be diagnosed during prenatal phase by means of genetic material assessment, biochemical assessment and early manifestations, and hence the pregnancy can be terminated. For example,

diagnosis of Down syndrome can be established prenatally by assessing increased foetal nuchal translucency, low AFP levels, and chromosomal aberration-Trisomy 21.

Since, the syndromes are multisystemic in manifestation; their management is always multidisciplinary, usually involving a team of paediatrician, cardiologist, neurologist, endocrinologist, ophthalmologist, audiologist, orthopaedic surgeon, dentist, physiotherapist, speech therapist, psychiatrist, occupational therapist, etc, as per the need of treating each symptom at different stages of disease. This approach can only provide a symptomatic treatment to the patient, but can never correct the root cause, especially a genetic defect, which is giving rise to all symptoms.

Screening / Diagnostic Tests	Advantages and Disadvantages
Preimplantation genetic diagnosis	Major advantage is the possibility of avoiding termination which can be extremely distressing for the couples concerned. However, complicating factors include a high rate of polyspermia, a small amount of DNA in polar bodies (making it difficult to amplify) and meiotic crossing-over, which can produce less definitive test results.
Ultrasonography	Carries no risk of miscarriage, however findings are not diagnostic. Moreover, abnormal findings may be transient, affected fetuses may not have detectable anomalies, and unaffected fetuses may show sonographic markers, simply as a matter of normal variation.
Maternal Serum Screen	Carries no risk to pregnancy but the diagnostic accuracy rate is only approximately 60%.
Chorionic Villus Sampling	Accuracy in diagnosis is 99%. If performed before 10 wks gestation carries risk of developing limb abnormalities in fetus. Although there are no conclusive data to link CVS performed at 10 to 12 wks gestation with limb abnormalities, it is reasonable to council patient of a possible risk as high as 1% births. There is higher likelihood of ambiguous results because approximately 1–2% of CVS samples reflect confined placental mosaicism, wherein the placenta, but not the fetus, contains both normal and abnormal cell lines.
Amniocentesis	Accuracy in diagnosis is 99%. Risk of complications or miscarriage is about 0.5% to 1%.
Percutaneous umbilical blood sampling	Failure rate to obtain fetal blood may be as high as 8.9%. The procedure-related fetal loss rate is estimated at 1–2%
Fetoscopy	Fetal mortality may be as low as 3% and long-term adverse sequelae have not yet been discovered.
Karyotyping	Culture failure can occasionally occur. Structural chromosomal abnormalities smaller than the achievable optical resolution cannot be detected. A mosaic can only be detected if chromosomally aberrant cells are present in the examined specimen.
Fluorescent in situ hybridization	Analysis for monogenic disorders is limited because the sequence of the specific genetic mutation must be known in order to apply the correct probe; and even when such a sequence is known, FISH may not identify a disorder if it is present in only a portion of the sample's cells (a 'mosaic' sample).
Direct DNA analysis	Require control DNA sequence which must be known before study. Moreover, only about 5% of disease-causing mutations affect known restriction sites, thus affecting which disorders may be analysed by restriction enzyme sequencing.
Linkage analysis	The prime advantage is that a specific gene, genetic sequence or gene product does not need to be known before study. Only molecular requirement is that the genetic disorder has been mapped to a general chromosome locus.
Biochemical tests	Possibility of both false positive and false negative results.

Table 10: Pitfalls in diagnosis

To overcome this, researchers in recent years have developed Gene Therapy, a technique for correcting defective genes responsible for disease development. This could be accomplished by[36,37]

- A normal gene may be inserted into a nonspecific location within the genome to replace a nonfunctional gene.
- An abnormal gene could be swapped for a normal gene through homologous recombination.
- The abnormal gene could be repaired through selective reverse mutation, which returns the gene to its normal function.

- The regulation (the degree to which a gene is turned on or off) of a particular gene could be altered.

Alternatively, replacement therapy can also be used in which the already defective gene product is replaced with a functional gene product. Example: Lesch-Nyhan syndrome.

Bringing up a child with special needs is difficult. The stress affecting the family make difficult to develop positive parent-child interaction, which in turn affects the child's overall development and hinders social adaptation. Hence, psychological support to family is one of the requisite in managing a syndromic child. This may be accomplished during early and pre-school period by means of early intervention and pre-school programmes run by various centres for syndromes such as Downside up (for Down syndrome, established in 1996, in Moscow). These centres provide psychological, pedagogical, social and informational support to the families of syndromic child.[38]

Conclusion

Early diagnosis is necessary for early intervention. Most of these craniofacial anomalies have oral manifestations, and many a times they are the only symptoms to present at particular stage. So we being dentist have a great social responsibility in identifying and diagnosing these craniofacial syndromes. Parental counselling is another important necessity, so as to provide them psychological and social support and to bring up their child in a favourable environment, making their existence into the real world.

Till now there is no complete treatment for genetic syndromes, rendering only symptomatic treatment by means of multidisciplinary approach. However, this could be achieved successfully if taken in direction of gene and replacement therapy, which targets to correct the defective gene and defective gene product respectively, hence correcting the root etiology.

Acknowledgements

We would like to acknowledge all the staff members of the department of oral and maxillofacial pathology for their support and cooperation.

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Source of Support: Nil, Conflict of Interest: None Declared.