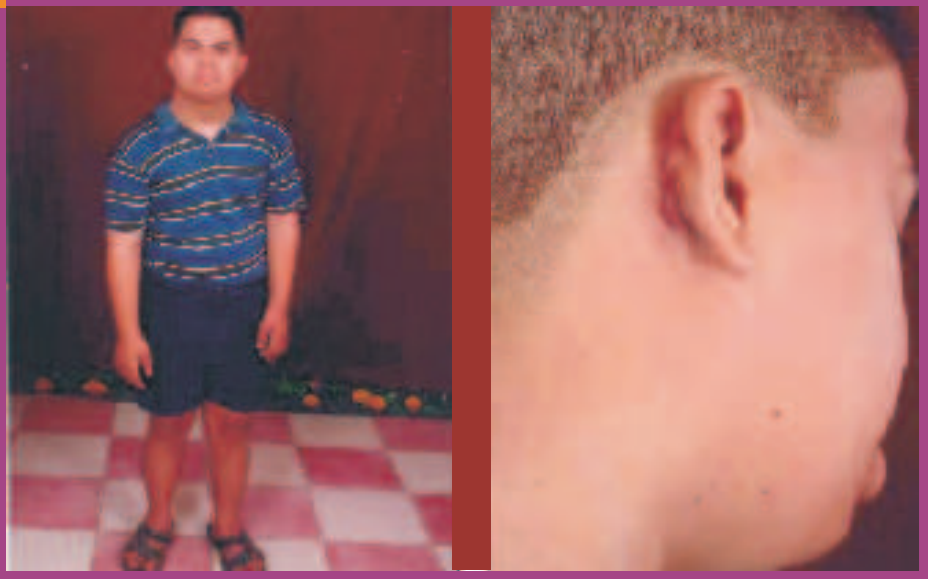
Syndromes Associated with Deafblindness



sense International (India)

Working with deafblind people throughout India

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Syndromes Associated with Deafblindness

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Acknowledgement

Sense International (India), with more than 14 years of work in the field of deafblindness has come in contact with thousands of students, professionals and family members having diverse information levels, personal goals, interests and needs. Some professionals and students are well acquainted with the term and disability 'deafblindness.'

However the present scenario reflects the need for more information on the part of medical professionals like paediatricians and other child specialists as they are unaware of different conditions and syndromes which are a major cause of deafblindness.

The purpose behind preparing this information book "*Syndromes Associated with Deafblindness*" is to provide a text that will help medical professionals understand some of the major causes of deafblindness, thus meeting the miscellaneous information needs of those involved in diagnosing, assessing and screening deafblind children. The concepts in this booklet can be used by a wide range of readers , from professionals to educators working with children/adults with deafblindness as well as individuals who are intellectually curious about the topic.

Special thanks to Dr. R.K.Hora, Asst. Professor, National Institute for the Mentally Handicapped, for finalizing the contents of this book. A very special mention and heartfelt thanks to all deafblind children and their families who have given the consent to share the information related to their condition and experiences, to support the information in this book and make it easier to understand. We would also like to thank our mentors and partner organizations who have shared their experiences, information and knowledge through different case studies.

We also thank Ms. Anna Daniel and Mr. Uttam Kumar for working on the content of this booklet and also for editing it.

We appreciate efforts of Mr. Shivkumar Sharma for designing the art lay out of the booklet.

Need of this booklet:

Deafblindness is considered to be a low incidence disability and in India there is a need for an increased number of educational services for this population. Many medical professionals do not diagnose deafblindness as a separate category of disability and many children with deafblindness end up in the programmes designed for hearing impaired or visually impaired or mentally challenged even though their needs are totally different from them.

This booklet has been prepared to target medical professionals like paediatricians, neonatologists, general physicians, referral doctors etc. to make them aware about deafblindness and syndromes associated with this unique condition.

This booklet will help the medical professionals to associate the medical condition with the disability of the child. This will also help them to understand the problems and needs of the children and refer the children to appropriate educational or rehabilitation services.

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Introduction to Deafblindness

Deafblindness is a combination of vision and hearing loss. It may seem that deafblindness refers to a total inability to see and hear. But, in reality, it is a condition in which there is a combination of visual and hearing impairments that cause "severe deficits in the areas of communication, orientation & mobility and accessing information". Children who are called deafblind are "educationally isolated" because impairments of sight and hearing require special and unique educational approaches to reach their full potential.

Though deafblindness is a low incidence disability, slowly this disability is getting recognition because of continued awareness in the community. It is estimated that there are more than 4,85,000 deafblind people in India. (Deafblind population calculated at 0.04% of the total population. This is based on the survey conducted in the UK by Sense as there is no survey or census done in India for deafblind people.)

Deafblindness is a condition presenting other difficulties than those caused by deafness or blindness. It is an "umbrella" term, which can include children, and adults who are:

- Blind and profoundly deaf
- Blind and severely or partially hearing impaired
- Partially sighted and profoundly deaf
- Partially sighted and severely or partially hearing impaired

Deafblindness is a distinct impairment that is more than simple vision loss and hearing loss. It is a unique impairment with specific effects on the lives of individuals. The difficulties created in communication, in mobility and in access to information are vast. The impact of a dual sensory loss is significantly different from a single loss as the individual's ability to compensate with the remaining sense is reduced. Many people will not be totally deaf and totally blind, but will have some remaining use of one or both senses. Others may also have additional physical and/or learning disabilities.

Historical Perspective:

The history of deafblindness in India can be traced back to the year 1977 when the first unit for deafblind was started in the Helen Keller Institute for the Deaf & Deafblind, Mumbai. There was very little awareness about deafblindness as in this vast country only 23 deafblind students were getting services through this institute. The situation was such that neither the Government, nor organisations working with disabled people were aware of deafblind population. Lack of awareness of this unique disability meant, and still means, that many deafblind people are left without support or labelled incorrectly (for example as severely mentally retarded) and receive inappropriate support.

This situation changed when Sense International (India) was established in the year 1997. With aim to support the development and establishment of more services for deafblind people throughout the country. Since then, Sense International (India) has been closely involved in the creation of services for deafblind people in different states of India. Sense International (India) is supporting 45 partner organisations in 20 States of India through a variety of service delivery models and training programmes. It has also established Regional Learning Centres in the four regions of the country situated in the North, East, West and South of India to provide assistance and technical support to the organisations working with single disability for initiating services in the field of deafblindness.

Though deafblindness presents many unique challenges to both, the individuals and to their caregivers and friends, these challenges are by no means insurmountable. Many persons who are deafblind have achieved a good quality of life. The persons who are deafblind and have high quality lives have several things in common. First, they have each, in their own way, come to accept the absence of sight and hearing as a life situation, which gives them a unique experience of the world. This fundamental acceptance can occur regardless of the severity of the particular sensory losses or other challenges that a person has. Second, they have had educational experiences and educational intervention at an early stage, which have helped them maximise their abilities to communicate and to function productively.

Finally, they live in families, communities, or social groups that have an attitude of welcoming acceptance. Now, India too has need-based services for deafblind people and soon these services can be availed by approaching any non-government or Government organisation in the state.

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Syndromes associated with deafblindness

Below is the list of the most common syndromes associated with deafblindness.

1	Aicardi syndrome	2	Alport syndrome
3	Alström syndrome	4	Apert syndrome
5	Bardet-Biedl syndrome	6	Batten Disease
7	CHARGE syndrome	8	Chromosome 18
9	Cockayne syndrome	10	Cogan's syndrome
11	Congenital Rubella syndrome	12	Cornelia de Lange syndrome
13	Craniosynistosis (Aipert, Crouzon and Pfeiffer)	14	Cri du Chat syndrome
15	Cytomegalovirus (CMV)	16	Dandy-Walker syndrome
17	DIDMOAD (Wolfram syndrome)	18	Down's syndrome
19	Foetal Alcohol syndrome	20	Flynn Aird syndrome
21	Friedreich's Ataxia (also known as Spinocerebellar degeneration	22	Goldenhar syndrome
23	Kearns - Sayre syndrome	24	Kaniest dysplasia
25	Marfan syndrome	26	Marshall syndrome

27	Marshall - Smith syndrome	28	Meningitis (viral and bacterial)
29	Metachromatic Leukodystrophy	30	Moebius syndrome (also known as Möbius syndrome)
31	Mohr - Tranebjaerg (also known as Deafness-Dystonia-Optic Neuronopathy syndrome)	32	Neurofibromatosis Type 2
33	Norrie Disease	34	Pallister Killian Mosaic syndrome
35	Peroxisomal Disorders (including Refsum Disease, Zellweger syndrome and Infantile Adrenoleukodystrophy)	36	Pierre-Robin syndrome
37	Stickler syndrome	38	Sturge - Weber syndrome
39	Treacher Collins syndrome	40	Trisomy 13 (also known as Patau syndrome)
41	Usher syndrome	42	Waardenburg syndrome
43	Wildervanck syndrome	44	Wolf-Hirschhorn syndrome (Trisomy 4p)

It is beyond the scope of this booklet to describe all of these syndromes in detail. The most prevalent syndromes, given in the table below, will be discussed in detail.

1	Alport syndrome	12	Marshall syndrome
2	Alstrom syndrome	13	Nf2 - Bilateral Acoustic Neurofibromatosis
3	Apert syndrome (Acrocephalosyndactyly, Type 1)	14	Norrie disease
4	Bardet- Biedl syndrome	15	Pfeiffer syndrome
5	Charge syndrome	16	Stickler syndrome
6	Congenital Rubella syndrome	17	Sturge – Weber syndrome
7	Cornelia de Lange syndrome	18	Treacher Collins syndrome
8	Crouzon syndrome (Craniofacial Dysotosis)	19	Trisomy 13 (Trisomy 13-15, Patau syndrome)
9	Down syndrome (Trisomy 21 syndrome)	20	Trisomy 18 (Edward syndrome)
10	Goldenhar syndrome	21	Turner syndrome
11	Kearns–Sayre syndrome	22	Usher syndrome

This list is in alphabetical order and not according to prevalence.

1. Alport syndrome

Alport syndrome is a generalised inherited disorder of the basement membranes, particularly those of the glomeruli, cochlea and eye caused by genetic mutations that affect the Type IV collagen. The earliest symptom of the disease is haematuria. Males present haematuria in early childhood, very often experience progressive sensorineural deafness with school age and usually develop, end stage renal disease in their early twenties with or without ocular abnormalities. Females present a variable clinical course and only a few of them are severely affected, because of an X-linked inheritance.

Characteristics:

- *Haematuria and Proteinuria*

  All affected patients, both males and females sometimes show features of microhaematuria. It may be detectable by one year of age in about 15% of cases, and by six years of age in about 70% of cases. Almost all males (98%) and 67% of females have proteinuria to some degree. High or increasing values of proteinuria imply poor prognosis.

- *Hypertension*

  It has been reported 75% of male and 35% of female patients present suffer from hypertension, very often in association with impaired renal function.

- *Renal Impairment*

  By an average age of 25 years, 94% of males and 3% of females present renal insufficiency with an elevated serum creatinine. However, progression to end stage renal failure occurs on 100% of males and only 15% of females.

- *Sensorineural Hearing Loss*

  Patients with Alport Syndrome usually present mild to moderately severe sensorineural hearing loss. Formal audiometric studies detect some level of hearing abnormality in about 85% of affected boys by age 15 years and many require hearing aids by the age of 25 years. Hearing loss is usually for frequencies above 3000Hz. This characteristic deafness is seen in 83% of males and 57% of females with an average deficit of 50-60 decibels.

- *Ophthalmic Lesions*

  Eye defects occur more frequently in male patients and ophthalmic lesions may precede the appearance of deterioration of renal function. About 25-30% of patients have a characteristic

abnormality of the shape of the lens (lenticonus), as well as changes in the retina. Although useful in diagnosis, these problems are not usually associated with severe loss of vision.

Prevalence:
Alport Syndrome affects about one in 5,000 persons (Sessa and Meroni, 2011)

Genetics:
Alport Syndrome is caused by defects in the chains of type IV collagen of the basement membranes. Type IV collagen is actually a family of six proteins, or chains, that are known as alpha-1 through alpha-6. Mutations that affect the alpha-3, alpha-4, and alpha–5 chains cause Alport Syndrome. The 3 genetic forms of Alport Syndrome are:

- XLAS (X-linked Alport Syndrome) – The most common form that accounts for 80% to 85% of the cases and results from mutations of the alpha-5 chain type IV collagen (gene COL4A5)
- ARAS (Autosomal Recessive Alport Syndrome) – This form accounts for 10% to 15% of the cases and is caused by mutations in the alpha-3 or alpha-4 chains (genes COL4A3 or COL4A4)
- ADAS (Autosomal Dominant Alport Syndrome) – Rare form that accounts for about 5% of the cases and is caused by mutations in the alpha-3 or alpha-4 chains (genes COL4A3 or COL4A4).

Diagnosis:
Gregory, M.C. et. al.(1996) has given the following 10 criteria for the diagnosis of Alport syndrome. 4 of the 10 criteria must be met:

1. Family history of nephritis of unexplained haematuria in a first degree relative of the index case or in a male relative linked through any numbers of females.
2. Persistent haematuria without evidence of another possibly inherited nephropathy such as thin Glomerular Basement Membrane (GBM) disease, polycystic kidney disease or IgA nephropathy.
3. Bilateral sensorineural hearing loss in the 2000 to 8000 Hz range. The hearing loss develops gradually, is not present in early infancy and commonly presents before the age of 30 years.
4. A mutation in COL4An (where n = 3, 4 or 5).

5. Immunohistochemical evidence of complete or partial lack of the Alport epitope in glomerular, or epidermal basement membranes, or both.

6. Widespread GBM (Glomerular Basement Membrane) ultrastructural abnormalities, in particular thickening, thinning and splitting.

7. Ocular lesions including anterior lenticonus, posterior subcapsular cataract, posterior polymorphous dystrophy and retinal flecks.

8. Gradual progression to ESRD (End Stage Renal Disease) in the index case of at least two family members.

9. Macrothrombocytopenia or granulocytic inclusions.

10. Diffuse leiomyomatosis of oesophagus or female genitalia, or both.

Differential Diagnosis:

MYH9 disorders (Epstein's syndrome and Fechtner's syndrome), Branchio-oto-renal syndrome, Thin basement membrane nephropathy, Maternally inherited diabetes and deafness

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2. Alstrom syndrome

(Alstrom syndrome is sometimes confused with Bardet-Biedl syndrome, which has similar symptoms. Bardet-Biedl syndrome tends to have later onset in its symptoms. The condition is also known as Alstrom-Hallgren syndrome after Alström's co-worker, the geneticist and psychiatrist Bertil Hallgren.)

Alstrom syndrome is a rare autosomal recessive condition characterised by multi-organ dysfunction. The key features are childhood obesity, blindness due to congenital retinal dystrophy, and sensorineural hearing loss. Associated endocrinologic features include hyperinsulinemia, early-onset type 2 diabetes, and hypertriglyceridemia. Thus, Alstrom syndrome shares several features with the common metabolic syndrome, namely obesity, hyperinsulinemia, and hypertriglyceridemia. Mutations in the ALMS1 gene have been found to be causative for Alstrom Syndrome with a total of 79 disorders-causing mutations having been described.

Characteristics:

Alstrom syndrome is characterized by cone-rod dystrophy, obesity, progressive sensory neural hearing impairment, dilated cardiomyopathy, the insulin resistance syndrome, and developmental delay. The first sign usually noticed in affected children is an involuntary rapid movement of the eye (nystagmus) and light sensitivity, which begins in infancy and eventually, leads to a degeneration of the retina (retinopathy) and blindness. Hearing impairment usually begins before the children are 10 years old. Later, in young adulthood, children become insulin resistant, develop high levels of insulin in the blood, and eventually type 2 diabetes mellitus.

Early symptoms

- Dilated cardiomyopathy in over 60% of cases, usually within the first few weeks after birth, but sometimes the onset is in adolescence or adulthood.
- Light sensitivity and vision problems (Cone-rod dystrophy) in all cases, usually within 15 months of birth and progressively worsening until about 20 years of age
- Developmental delays in 50% of cases, learning disabilities in about 30% of cases
- Obesity in 100% of cases, apparent by 5 years of age, but often apparent in infancy (Alstrom infants usually have normal birth weights, and by

adolescence, weights tend to be in the high-normal to normal range)

Further symptoms

- Progressive hearing loss
- Kidney problems
- Liver problems
- Insulin resistance/Type 2 diabetes

Prevalence:
Alstrom Syndrome has an estimated prevalence of <1 in 100,000 (Joy et. al., 2007).

Genetics:
Alstrom syndrome is an autosomal recessive disorder caused by a mutation in a gene located on chromosome 2 (2p13). The mutated gene, known as ALMS1, codes for the production of a protein whose function is still not fully known.

Diagnostics:
Marshall et. al. provided a comprehensive guidance for diagnostic criteria in their 2007 publication.

Birth – 2 years:
Minimum diagnosis requires 2 major criteria or 1 major and 2 minor criteria.

Major criteria are:

1) ALMS1 mutation in 1 allele and/or family history of Alstrom Syndrome
2) Vision pathology (nystagmus, photophobia).

Minor criteria are:

1) Obesity
2) Dilated cardiomyopathy with congestive heart failure.

Other variable supportive evidence: Recurrent pulmonary infections, normal digits, delayed developmental milestones.

At 3–14 years of age:

2 major criteria or 1 major and 3 minor criteria.

Major criteria are:

1) ALMS1 mutation in 1 allele and/or family history of Alstrom Syndrome,
2) Vision pathology (nystagmus, photophobia, and diminished acuity). If old enough for testing: cone dystrophy by ERG.

Minor Criteria:

1) Obesity and/or insulin resistance and/or Type 2 Diabetes
2) History of dilated cardiomyopathy with congestive heart failure
3) Hearing loss
4) Hepatic dysfunction
5) Renal failure
6) *Advanced bone age*

Variable supportive evidence: Recurrent pulmonary infections, normal digits, delayed developmental milestones, hyperlipidemia, scoliosis, flat wide feet hypothyroidism, hypertension, recurrent urinary tract infection, growth hormone deficiency.

Presentation 15 years – adulthood:

2 major and 2 minor criteria or 1 major and 4 minor criteria.

Major criteria are:

1) ALMS1 mutation in 1 allele and/or family history of Alstrom Syndrome.
2) Vision pathology (history of nystagmus in infancy/childhood, legal blindness, and cone and rod dystrophy by ERG).

Minor criteria:

1) Obesity and/or insulin resistance and/or Type 2 Diabetes
2) History of dilated cardiomyopathy with congestive heart failure.
3) Hearing loss
4) Hepatic dysfunction
5) Renal failure
6) Short stature
7) Males: hypogonadism, Females: irregular menses and/or hyperandrogenism

Other supportive features: Recurrent pulmonary infections, normal digits, history of developmental delay, hyperlipidemia, scoliosis, flat wide feet, hypothyroidism, hypertension, recurrent urinary tract infections/urinary dysfunction, growth hormone deficiency, alopecia.

Differential Diagnosis:

Bardet–Biedl syndrome (BBS), Leber congenital amaurosis (LCA), and idiopathic cardiomyopathy in infants.

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3. Apert syndrome (Acrocephalosyndactyly, Type 1)

Apert syndrome is a form of acrocephalosyndactyly, a congenital disorder characterized by craniosynostosis, craniofacial anomalies, and severe symmetrical syndactyly of the hands and feet. It is classified as a branchial arch syndrome, affecting the first branchial (or pharyngeal) arch, the precursor of the maxilla and mandible

Characteristics:

The inherited form of Apert syndrome is transmitted as an autosomal dominant trait. Many of the bony sutures of the skull close prematurely, giving the head a distorted shape. The face is peculiar looking and full-length webbing or fusion may occur between the 2nd, 3rd and 4th fingers, as well as the toes. The bones in the hands and feet become progressively fused, reducing flexibility and function. There is variable retardation with intellectual development. Children with Apert's may also have one or more of these abnormalities like visual problems due to eye muscle imbalance; hearing loss due to frequent infections; severe acne; mild mental retardation; cleft palate;hyperactive sweat glands.

Prevalence:

Apert syndrome occurs in approximately 1 in 50,000 live births (Lajeunie, 2005). Cohen et al (1992) estimated prevalence at 1in 65,000 (approximately 15.5 in 1,000,000) live births. Asians have the highest prevalence of 22.3 cases per million live births (Tolarova et. al., 1997).

Genetics:

Apert Syndrome is caused by a genetic mutation in the FGFR2 (fibroblast growth factor receptor 2) gene. More than 98% of cases with Apert syndrome are caused by specific missense substitution mutations, involving adjacent amino acids (i.e., Ser252Trp, Ser252Phe, Pro253Arg) in the linker between the second and third extracellular immunoglobulin domains of FGFR2, which maps to chromosome bands 10q26. The remaining cases are due to Alu-element insertion mutations in or near exon 9 of FGFR2.

Diagnosis:

1. A skull x-ray and physical exam can confirm the diagnosis of craniosynostosis.
2. Hand or foot x-rays are also very important to determine the extent of bone problems.
3. A genetic test for mutations in the fibroblast growth factor receptor 2 gene can confirm the diagnosis of Apert syndrome.
4. Hearing tests should also always be performed.

Differential Diagnosis: Crouzon syndrome, Pfeiffer Syndrome

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4. Bardet-Biedl syndrome (Laurence Moon-Bardet-Biedl syndrome (LMBBS))

Bardet-Biedl syndrome is a rare inheritable condition characterised by the pentad of obesity, mental retardation, pigmentary retinopathy, polydactyly and hypogenitalism.

Characteristics:

The accepted major criteria for diagnosis include retinal dystrophy, obesity, polydactyly, male hypogonadism, mental retardation, and renal dysfunction. In addition to the primary features, a number of associated secondary features, including neurological, speech, and language deficits, auditory deficiency, behavioural traits, facial dysmorphism, and dental anomalies have been identified. The motor problems identified include delay in acquisition of motor skills, unsteady gait, and ataxia. Language development is delayed in many cases, although this may be commensurate with overall intellectual function, and there are also reports of speech problems that include articulation difficulties, consonant omission or distortions, dysarthria and hypernasality. Developmental delay has been widely described as a major feature of BBS, with two-thirds to three-quarters of patients performing in the mental retardation range on formal testing.

Prevalence:

Prevalence rates range from 1 in 100 000 to 1 in 160 000, although there are communities in which BBS appears to be more common as a result of consanguinity (Beales et. al., 2001)

Genetics:

Bardet- Biedl syndrome is transmitted in an autosomal recessive manner. Mutations in 14 genes are known to be associated with BBS: BBS1, BBS2, ARL6/BBS3, BBS4, BBS5, MKKS/BBS6, BBS7, TTC8/BBS8, B1/BBS9, BBS10, TRIM32/BBS11, BBS12, MKS1/BBS13, and CEP290/BBS14. Mode of inheritance is through autosomal recessive mode.

Diagnosis:

The diagnosis of Bardet-Biedl syndrome (BBS) is established by clinical findings. Beales et. al. [1999] and Beales et. al. [2001] have suggested that the presence of four primary features or three primary features plus two secondary features is diagnostic.

Primary features: Four features are required to be present of:

- Rod-cone dystrophy
- Polydactyly

- Obesity
- Learning disabilities
- Hypogonadism in males
- Renal anomalies

OR

Three primary plus two secondary features are required of:

Secondary features:

- Speech disorder/delay
- Strabismus/cataracts/astigmatism
- Brachydactyly/syndactyly
- Developmental delay
- Polyuria/polydipsia (nephrogenic diabetes insipidus)
- Ataxia/poor coordination/imbalance
- Mild spasticity (especially lower limbs)
- Diabetes mellitus
- Dental crowding/ hypodontia/small roots/high arched palate
- Left ventricular hypertrophy/congenital heart disorder
- Hepatic fibrosis

Differential Diagnosis: McKusick-Kaufman syndrome, Alstrom syndrome, Joubert syndrome, Leber congenital amaurosis, Senior-Loken syndrome, Biemond syndrome type II

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5. CHARGE Syndrome (Abruzzo-Erickson Syndrome)

CHARGE syndrome was initially defined as a non-random association of anomalies (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness). In 1998, an expert group defined the major (the classical 4C's: Choanal atresia, Coloboma, Characteristic ears and Cranial nerve anomalies) and minor criteria of CHARGE syndrome. Individuals with all four major characteristics or three major and three minor characteristics are highly likely to have CHARGE syndrome.

Characteristics:

Coloboma mainly affects the retina. Major and minor congenital heart defects (the commonest cyanotic heart defect is tetralogy of Fallot) occur in 75 to 80% of patients. Choanal atresia may be membranous or bony; bilateral or unilateral. Mental retardation is variable with intelligence quotients (IQ) ranging from normal to profound retardation. Under-development of the external genitalia is a common finding in males but it is less apparent in females. Ear abnormalities include a classical finding of unusually shaped ears and hearing loss (conductive and/or nerve deafness that ranges from mild to severe deafness). Multiple cranial nerve dysfunctions are common. There are many challenging behaviours that are expressed in individuals with CHARGE syndrome. Children with CHARGE syndrome have relatively low adaptive behaviour skills and motor impairments being particularly significant, with symptoms of autistic spectrum disorder (ASD). The behaviour they display is often very adaptive to their environment and to their own disabilities. These behaviours may be partially related to problems with arousal and self-regulation.

Aetiology:

There is a crucial stage of embryogenesis, when failure to rupture the primitive bucconasal membrane (35th to 38th day) brings about choanal atresia. Conotruncal cardiac defects can result from aberrations in cephalic neural crest cell migration during the 4th and 5thweeks after conception. The cochlear duct begins to develop around the 36th day, and the eyes develop between days 34 and 44 days post-conception, which is also the time during which many cranial nerves are developing. All the malformations in CHARGE syndrome occur early during the first trimester. In situ hybridization analysis of the CHD7 gene during early human development showed a good correlation between CHD7 expression patterns and the developmental anomalies observed in CHARGE syndrome (Sanlaville et al, 2005).

Prevalence:

The reported incidence of CHARGE syndrome ranges from 0.1 to 1.2 per 10,000 and depends on professional recognition (Blake and Prasad, 2006).

Genetics:

Gene map locus 8q12.1, 7q21.1.

CHARGE syndrome is an autosomal dominant condition affecting males and females equally but it has been suggested that deficiency in migration of neural crest cells, deficiency of mesodermal formation, or defective interaction between neural crest cells and mesoderm play a part in these defects of blastogenesis. Most cases of CHARGE syndrome arise de novo (anew). However parents of affected individuals may be carriers. The recurrence risk for unaffected parents is approximately 1-2%. Many patients with CHARGE syndrome have a microdeletion at 8q12.1. Of those in whom a micro deletion is not detected, 59% have a mutation detectable by sequence analysis in the CHD7 gene. Published mutations in CHD7 are scattered throughout the gene and include missense, nonsense, and splicing mutations. All malformations occur in the first trimester.

Diagnosis:

A diagnosis of CHARGE syndrome should be considered in any neonate with coloboma, choanal atresia, asymmetric facial palsy or classical CHARGE ears in combination with other specific congenital anomalies. Individuals with all four major characteristics (the classical 4C's: Choanal atresia, Coloboma, Characteristic ears and Cranial nerve anomalies) or three major and three minor characteristics are highly likely to have CHARGE syndrome.

Diagnostic criteria for CHARGE syndrome

Features of CHARGE syndrome		**Later childhood/adolescent issues**
	Major "4 C's"	
Ocular Coloboma	Coloboma – of iris, retina, choroid, disc; microphthalmia	Photophobia; retinal detachment
Choanal atresia/stenosis	Choanal atresia (or Cleft palate) –unilateral/bilateral, membranous/ bony, stenosis/atresia	Facial growth problems, recurrent closure and resurgeries, unilateral nasal discharge
Cranial nerve anomalies	Cranial nerve dysfunction – Facial palsy (unilateral or bilateral), Sensorineural deafness and/or swallowing problems	Feeding/swallowing problems;

Characteristic ear anomalies	Characteristic ear abnormalities – External ear (lop or cup shaped), Middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects	Progressive hearing loss; chronic middle ear infections; vestibular problems affecting balance and /or motor skills.
	Minor	
Cardiovascular malformations	Cardiovascular malformations – All types: especially conotruncal defects (e.g. Tetralogy of Fallot), AV canal defects, and aortic arch anomalies	Arrhythmias; angina; further cardiac surgeries
Genital hypoplasia	Genital hypoplasia – Males: Micropenis, cryptorchidism, Females: Hypoplastic labia, Both: Delayed incomplete pubertal Development	Pubertal delay, hormone replacement; fertility (unsure)
Cleft lip/palate	Orofacial cleft – Cleft lip and/or palate	Cosmetic concerns; self-image
Tracheoesophageal-fistula	Tracheoesophageal-fistula – Tracheoesophageal defects of all types	Reflux oesophagitis; feeding/swallowing problems
Distinctive CHARGE facies	Characteristic face -- sloping forehead, flattened tip of nose	Cosmetic concerns; self-image
Growth deficiency	Growth deficiencies – Short stature	Growth hormone (GH) replacement Borderline GH stimulation tests
Developmental delay	Developmental delay – Delayed motor milestones, language delay, mental retardation (MR)	Educational, behavioural, social adjustment issues; Autistic-like problems
	Occassional	
Renal anomalies	Duplex, Reflex	Renal failure
Spinal anomalies	Scoliosis; Osteoporosis	Scoliosis
Hand anomalies		Fine motor problems; cosmetic concern
Neck/shoulder anomalies		Self-image concern

Lawand , Graham, Prasad, and Blake (2003).

Differential Diagnosis:
VACTERL association, DiGeorge sequence, Velocardiofacial syndrome (VCFS), Cat Eye Syndrome, retinoic acid embryopathy, and PAX2 abnormalities

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CASE STUDY

CHETNA

16 years ago, a little girl was born in a small village, Bala, in the deep recesses of Gujarat's Surendranagar district. Her parents lovingly named her Chetna, which meant life, vitality. To their disappointment, the little girl hardly showed any signs of vitality… for the next three years little Chetna had a strange existence where she was not able to sit, walk or even eat food. The little child was diagnosed to be suffering from a congenital condition called CHARGE syndrome that left her profoundly deafblind by birth.

Her helpless father a black smith by profession, made an iron chair where she would be strapped, lost in her incommunicable world. It was at this time that providence intervened and Chetna was exposed

to the home based training programme for deafblind by Sense International (India). Though she did put up an initial resistance, Chetna eventually accepted her teacher, Deepak as he took her by her fingers and embarked on the exploratory journey of life.The next eleven odd years have witnessed a transformation in Chetna. Today she not only rings in cheer in her own house as she runs about, she can even go to the neighbourhood grocery shop to buy her favourite sweets. She loves dressing up and takes all her time to decide what she is going to wear that day. Not only can she take care of her own needs by herself, she goes ahead and helps her mother in daily chores such as sweeping and mopping the floor, and even serving the guests with water and hospitality. She even knows how to make tea! If you are lucky, she may just roast some chana for you.

She often takes a walk to the village pond with her teacher where she loves to play with the other children. Motivated by her yearning to learn, the educator convinced the local school to admit her too. Every day, Chetna packs her own bag enthusiastically, gets ready and runs to the school. She joins in the morning prayer with her class mates in her own unique way and shares her snacks with them. She tries to emulate them at every step and has already begun to learn numbers and colours.

That little chair with straps that her father made, a grim reminder of what life could have been, is relegated to a corner in her house. For, after all, “Chetna”, her name, stands for unbridled life, and vivacity… may be that is why her parents named her Chetna.

6. Congenital Rubella Syndrome

Congenital rubella syndrome (CRS) is a group of anomalies that an infant may present as a result of maternal infection and subsequent foetal infection with rubella virus.

Characteristics:

The main defects caused by rubella infection are: sensorineural deafness, which can progress after birth; various ocular abnormalities such as cataract, retinopathy or glaucoma; cardiovascular defects; which can occur at any time after infection between the 3rd and 12th week of gestation, and the most common defects include patent ductus arteriosus, stenosis of the pulmonary artery and its branches, and septal defects; brain damage, that only occurs after infection between the 3rd and 16th week of gestation, causing mild to severe mental retardation with microcephaly and spastic diplegia; major structural malformations are rare.

Any combination of the above-mentioned list of defects in a context of maternal rubella is called congenital rubella syndrome (CRS). A constant feature of CRS is foetal growth retardation; Infection occurring between the fifth month and the end of pregnancy or later does not usually cause disability, although cases of deafness have been reported after infection as late as 28 weeks, and peripheral pulmonary artery stenosis as late as 23 weeks.

Long-term follow-up of newborn with CRS s has revealed that they are at increased risk of late onset chronic diseases such as insulin-dependent diabetes (risk 50 times higher than that in the general population), thyroid dysfunction, digestive disturbances, and a rare neuro-degenerative disorder called panencephalitis. These conditions may result from ongoing viral infection, or autoimmune response.

The clinical features of CRS, including some of the delayed manifestations of disease, which may not present until adolescence or adulthood, can be classified as transient, self-limiting, or permanent. Some developmental defects such as deafness might not become apparent for months or even years, but then can persist indefinitely. Between ages 3 and 12 months, some infants with CRS develop multisystem condition with a chronic rubella-like rash, persistent diarrhoea and pneumonitis, which is also, although inappropriately, referred to as late-onset condition. Circulating immune complexes and interstitial pulmonary deposits may be present. This form of disease might respond to treatment with corticosteroids. The burden of deafness among infants with CRS has certainly been underestimated; deafness is probably the most important cause of non-genetic congenitally acquired hearing loss in countries with no rubella vaccination programme. Methods to assess hearing loss in early infancy,

such as Otoacoustic emissions and auditory brainstem responses, are now available to screen infants at risk and will detect hearing defects much earlier than previously, even neonatally. The equipment is, however, costly and has not been fully assessed for reliability outside the laboratory or been widely used. This lack of evidence limits the use of such techniques in developing countries where CRS is common.

Aphakic glaucoma can occur after cataract aspiration, and neo vascularisation of the retina might be a late-onset manifestation of CRS. In some imaging studies enlargement of lateral ventricles and reduced grey matter, intracranial calcification, and linear hyper echogenicity in the basal ganglia region have been reported; these lesions might predict the development of microcephaly.

Pathogenesis:

Foetal damage is multi factorial, resulting from a combination of rubella-virus-induced cellular damage and the effect of the virus on dividing cells. Placental infection occurs during maternal viraemia, results in focally distributed areas of necrosis in the epithelium of chorionic villae and in the endothelial cells of its capillaries. These cells seem to be desquamated into the lumen of vessels, suggesting that rubella virus is transported into the fetal circulation as infected endothelial cell emboli, which may result in infection and damage of foetal organs. During early pregnancy, foetal defence mechanisms are immature, and a characteristic feature of rubella embryopathy in early gestation is cellular necrosis in the absence of any inflammatory response.

Rubella-virus-infected cells have a reduced life span in the organs of affected foetuses and infants; the number of cells is lower than in healthy infants. Rubella virus can also induce damage by apoptosis. In-vitro studies suggest that this effect is due to a rubella-induced capsase dependent mechanism. The exact mechanism has yet to be determined, but it seems to be dependent on virus replication started within 12 hours of infection.

Prevalence:

The average estimated CRS in India is 123 per 100 000 live births (Cutts and Vynnycky, 1999).

Laboratory diagnosis:

The diagnosis of congenitally acquired rubella is made by;

1. The presence of rubella IgM (Immunoglobulin M, an antibody against rubella) in cord blood or serum samples taken in infancy.

2. Detection of rubella antibodies at a time when maternal antibodies should have disappeared (approx. six months of age)
3. Isolation of rubella virus from infected infants in the first few months of life.

Differential Diagnosis: Cytomegalovirus, toxoplasmosis, herpes simplex, varicella zoster

Vaccination:

Rubella vaccination makes CRS a preventable disease. Live attenuated rubella vaccines were first licensed in the 1960s (panel). RA27/3, which is grown in human diploid cells, is now used in most of the world, although China and Japan use similar locally developed live attenuated vaccines. Immune responses to rubella vaccine closely resemble those of naturally acquired infection. More than 95% of recipients older than 11 months seroconvert and antibody responses are detectable for more than 21years. Long-term vaccine efficacy is more than 90%. However, in some vaccines, antibody concentrations might wane over time to less than 10 IU/mL. Studies in which volunteers with low or undetectable concentrations of antibody were challenged intranasally with high-titre rubella vaccine showed boosts in antibody, but viraemia was rare, transient, and of low concentration. The duration and degree of viraemia is unlikely to result in foetal damage. Indeed, inadvertent rubella vaccination among susceptible women in early pregnancy does not lead to rubella-induced defects. Thus, analysis of data from several countries identified no CRS cases. The theoretical maximum risk of rubella-induced major malformations among infants whose mothers were susceptible and vaccinated during the first 2 months of pregnancy, was calculated to be 1·3%, which is less than the risk of major malformation occurring in usual pregnancies (3%). In recent rubella campaigns in Brazil, which included women of childbearing age, more than 6000 pregnant women were inadvertently vaccinated. Vaccination causes few side-effects but it is associated with acute joint symptoms in up to 40% of post pubertal females, there being a higher frequency of HLA-DR2 and HLA-DR5 and lower frequencies of HLA-DR4 and HLA-DR6 in RA27/3 vaccines with arthropathy. Hormonal changes are also suggested to be involved. As with other live vaccines, rubella vaccine should not be given to immunocompromised patients. Nevertheless, since rubella vaccine is generally administered as the MMR vaccine given at 15 months of age, HIV-positive individuals, particularly children, should benefit from being afforded protection, not only from rubella, but from mumps and measles; measles is life-threatening in such patients.Current US guidelines state that people who are HIV positive, who are asymptomatic or have only mild symptoms can be vaccinated since they do not generally experience complications.

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CASE STUDY

Shazia Fathima is a young adult with Congenital Rubella Syndrome. Now at 16, she is a pretty young lady, shy but full of confidence, quiet yet vociferous when she needs to make her point clear. She is very focussed on what she wants to be when she is out of school -an astronaut. This is her dream which her parents and her present teacher will see that it comes true. Shazia has varied interests especially in academics, her favourite being to know about various countries and also wanting to wander in the forests of Africa and see the snowy peaks of the world's great mountains. She is well informed about natural calamities like tsunami, earthquakes and global warming.

Her favourite hobby as all young girls of her age is to browse through fashion magazines and also to design her clothes. She is interested in beauty tips and jewellery. Shazia is good in embroidery, screen printing on fabric and macramé. She can do all this on her own despite her low vision.

When asked to do fabric printing on tee shirts, she is able to choose the appropriate pattern based on whether it is for women, men or children, choose the colours and then do the printing. She is now learning quilling.Shazia enjoys doing SUDOKO and word searches. She is adept at sign language and enjoys jokes, stories and movies. Her favourite television programme is WWF and she reads the newspaper from the first to the last page .She makes sure that she understands each and every thing she reads.

Her greatest achievement is her presentation in the National Conference on Deafblindness held in New Delhi in January this year. She is encouraged by her family at home who do not think of her as a person with disabilities. At school, she emerges as one of the best pupils .Her ambition is to posses a laptop of her own. We all hope that soon this dream among many others will bear fruit. As teachers we wish that she completes her High School with good grades. Shazia Fathima is an example of a person who has reached this level braving all odds-the odds of having dual sensory impairment-deafblindness.

Inputs by

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- Deepika Srinivasan

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7. Cornelia de Lange Syndrome

Cornelia de Lange syndrome (CdLS) is a syndrome of multiple congenital anomalies characterized by a distinctive facial appearance, prenatal and postnatal growth deficiency, feeding difficulties, psychomotor delay, behavioural problems, and associated malformations that mainly involve the upper extremities. It has been reviewed recently and the clinical dichotomy into “classical” and “mild” cases is now generally accepted. Those in the mild group show less retardation of growth and intellect. They seldom have the more severe limb reduction defects or congenital heart defects, although the characteristic facial features may be the same in both groups.

Characteristics:

The principal clinical characteristics of this syndrome are the delay in growth and development, hirsute, anomalies in the structure of the limbs and distinctive facial characteristics.

Hypo-growth is at first intrauterine and very intense, with delays in osseous maturation and grave, hypertonic mental deficiencies (100% of the cases). At birth and during the length of their life, these patients present a weight and size inferior to that corresponding to their age.

The facial features are distinctive, with microcephaly, synophrys, hirsutism, low set ears, small nose with antiverted nares, small widely spaced teeth, full philtrum, thin lips, and perioral cyanosis. IQ ranges from below 30 to 102 with an average of 53. Many individuals demonstrate autistic and self-destructive tendencies. Frequent findings include cardiac septal defects, gastrointestinal dysfunction, hearing loss, myopia, and cryptorchidism or hypoplastic genitalia.

The extremities are also usually altered by the presence of simian palm groove, limited mobility of the elbow, micromelia, and syndactyly.

Ocularly they may present palpebral ptosis, conjunctivitis or chronic blepharitis, stenosis of the palpebral canal, severe myopia, and nystagmus.

Prevalence:

Prevalence of this syndrome is between 1/10,000 and 1/60,000 in neonates. There is no racial predilection. It is slightly more common in females as compared to males (F: M:: 1.3:1) (Grau-Carbó et. al., 2007).

Genetics:

This syndrome is considered to have an autosomal dominant pattern of inheritance. NIPBL and SMC1A (formerly SMC1L1) are the only genes currently known to be associated with CdLS. Mutations in NIPBL are identified in 50% of individuals with CdLS. The Mutations in the other two genes are much less common. Mutations in SMC1A are identified in a small percentage of individuals with a clinical diagnosis of CdLS.

Diagnosis:

Diagnosis of CdLS is clinically based on the presence of craniofacial features, growth failure, intellectual disability, limb abnormalities, and hirsutism. Molecular genetic testing is clinically available.

Differential Diagnosis: Foetal Alcohol syndrome

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8. Crouzon syndrome (Craniofacial Dysostosis)

Crouzon syndrome is an inherited syndrome of craniofacial dysmorphology, or abnormal craniofacial appearance, which was originally described in 1912 and is now well recognized. Children' who have Crouzon syndrome have a range of problems of variable severity, from mild facial symptoms causing a primarily cosmetic concern, to severe symptoms affecting breathing, feeding, vision and brain development.

Characteristics:

Crouzon syndrome is characterized by premature closure of the cranial sutures, midface hypoplasia, orbital deformities, and other occasional associated abnormalities. The abnormal skull shape is usually noted in the newborn period although, occasionally, it may be detected either prenatally or not until later in infancy. The triad composed by cranium deformities, facial anomalies and exophthalmia, described by Crouzon in 1912, forms today the Crouzon syndrome.

In the face, the commonest features are a maxillary hypoplasia and shallow orbits which may be present at birth or become more evident as the childhood progresses. Dentition is also affected, and this requires specialist orthodontic care; which is dependent on good general dental care at home. Rarely, there may be palate problems. Seen from the side, the face has a concave appearance, and the shallow orbits result in prominent eyeballs or 'proptosis'. Optical atrophy may be a complication resulting from the narrow optical channel. Blindness following the optical atrophy by the intracranial hypertension may also occur. Other characteristics generally seen in these patients are visual disturbances relating to a muscular unbalance.

The conductive hearing loss is common due to middle ear deformities. Alterations to the clamp with consequent fusion in the promontory, hearing ossicle ankylosis heading to the epitympanus external wall, distortions and narrowing of the middle ear space, absence of tympanic membrane and external channel stenosis or atresia are possible due to deforming growth. Recurrent infections are common in the hearing system.

Prevalence:

Crouzon syndrome is believed to affect 1 in 25,000 people 000 people worldwide (Maloth et. al, 2010)

Genetics:

Crouzon syndrome is transmitted in an autosomal dominant pattern. The mutation in the genes that

codify receptor 2 of the (FGFR2) fibroblast growth factor is responsible for the deformities observed.

Twenty five mutations have already been identified in the FGFR2 and concern the Crouzon Syndrome pathogenesis. Even though it has an autosomal dominant inheritance, 50% of the Crouzon syndrome incidents are not inherited but result from new spontaneous mutations.

Diagnosis:

Diagnosis of Crouzon syndrome usually can occur at birth by assessing the signs and symptoms of the baby. Further analysis, including radiographs, magnetic resonance imaging (MRI) scans, genetic testing, X-rays and CT scans can be used to confirm the diagnosis of Crouzon syndrome.

Differential Diagnosis:

Apert Syndrome, Pfeiffer syndrome, Carpenter syndrome, Saethre- Chotzen syndrome

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9. Down syndrome (Trisomy 21 syndrome)

Down syndrome, named after John Langdon Down who identified the syndrome, is one of the more common chromosomal disorders and includes some degree of mental defect. It is caused by the presence of an additional chromosome 21, causing the affected person to have three and not the normal 2 chromosomes and hence is referred to as Trisomy 21.

Characteristics:
Muscle hypotonia; flat facial profile, including a somewhat depressed nasal bridge and small nose, oblique palpebral fissures, dysplastic ears, simian crease, joint hypermobility, fifth finger has one bending joint instead of two (dysplastic middle phalanx), epicanthal folds, excessive space between large and second toe (sandal gap); enlargement of tongue in relationship to size of mouth.

Health concerns for individuals with Down syndrome include a higher risk for congenital heart defects, gastroesophageal reflux disease, recurrent ear infections, obstructive sleep apnoea, and thyroid dysfunctions.

Facial characteristics:
Midface dysplasia leading to

- nose malformations including a flat broad bridge
- ear malformations including “lop” ears, low set ears and ears with a flat or absent helix
- eye malformations: Epicanthal folds with slanting almond shaped eyes, strabismus, nystagmus and refractory errors
- Brachicephaly (broad, short head) and lack of supraorbital ridges and hypotelerism (secondary to hypoplasia of central face)
- Absence of frontal sinuses and absent or reduced maxillary sinuses
- Nasal septum or nasal conchal deviations

Medical conditions like congenital cardiopathy, upper respiratory tract infections, Alzheimer dementia and atlanto- axial instability are also common.

Other medical problems include speech impairment, hearing impairment, visual impairment, hypotonia, obesity, below average height, dry rough scaly skin and a single palmar crease (simian crease).

Prevalence:

A meta-analysis of studies of births at hospitals in India revealed the incidence of Down Syndrome to be 1 in 820 newborns. The incidence increases with advancing maternal age risinf from 1 in 1528 at age 20 to 1 in 184 at age 35, and 1 in 112 at age 40 years (Verma,, Kabra and Arun, 1996)

Genetics:

The aetiology of Down syndrome relates to the problem of nondisjunction of a 21 chromosome during oogenesis, thus an extra 21 chromosome is provided to the offspring by the mother. Recent studies also implicate paternal aetiology through nondisjunction during spermatogenesis. There are three types of Down syndrome, although it is generally thought that there is no clinical difference in the three genotypes.

(1) Trisomy 21 (94%): The extra 21 chromosome (three instead of the usual two) produces a complement of 47 chromosomes. Trisomy 21 may also be referred to as Trisomy G.

(2) Translocation (5%): A segment of a 21 chromosome is found attached to other pairs of chromosomes (usually #14, thus referred to as a 14/21 translocation). These individuals have the normal complement of 46 chromosomes.

(3) Mosaicism (1%): Nondisjunction occurs at a later stage of cell division; therefore, some cells have the normal complement of 46 chromosomes and other cells 47 chromosomes (with an extra 21 chromosome).

Diagnosis:

In 70-75% of foetuses with Down syndrome, increased nuchal translucency can be seen on first-trimester ultrasonography. On the second-trimester examination, malformations (essentially heart and digestive) are present in 60% of the cases, and can be associated with minor morphological signs. Prenatal diagnosis can be confirmed by foetal karyotype on amniocentesis or chorionic villous sampling. Postnatally diagnosis can be confirmed by karyotyping.

Differential Diagnosis: Trisomy 18, Multiple X chromosomes

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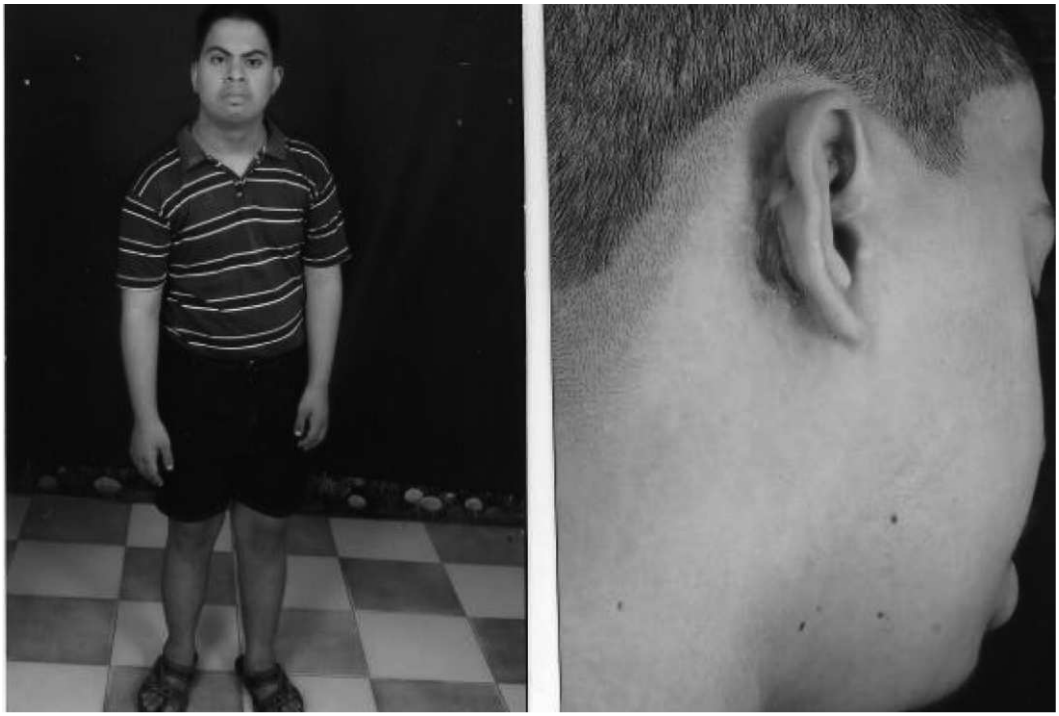
CASE STUDY

Tinku



Tinku is a 19 years old young adult with Down syndrome and deafblindness. His birth cry was delayed. He got pneumonia when he was 15 days old. Tinku was identified as developmentally delayed at the age of 6 months. He started sitting when he was 3 years old and walking at 5 years.

He was admitted to Association for the Welfare of Handicapped, Faridabad when he was 7 years old. A year later, he was admitted to boarding where detachment in his retina was diagnosed in both of his eyes. He again came back to AWH, Faridabad.

In year 2002, he started having discharge for his right ear. He was operated twice for that but surgery was not successful. In 2006, eye surgery for retinal detachment was performed but it was also not successful. He is having partial vision and partial hearing but both his vision and hearing is deteriorating now.

With educational intervention and parental support and cooperation, Tinku is now independent in all of his self care tasks and helps in home based activities. He enjoys music and dance. His socialisation skills have improved and he loves to interact with teachers and peer group.

Now, Tinku has a small shop “Tinku di Hatti” where he sells snacks, biscuits and chocolates. He loves to interact with the children and the people who comes to his shop. With the help of his teacher, Tinku also sets up a shop in the school.

And every evening, before going home, Tinku takes some chocolates from his shop to give to his little neice who adores Tinku and loves to play with him.

10. Goldenhar syndrome *(Oculoauriculovertebral {OAV} Dysplasia, Facioauriculovertebral Sequence,Oculoauriculovertebral Spectrum)*

Goldenhar syndrome is a rare presumably inherited condition, which has a multifactorial aetiopathology that also includes nutritional and environmental factors that can result in disturbances of blastogenesis involving the first and second branchial arches and involves deformities of the face, ear and vertebrae.

Characteristics:

- Facial asymmetry, hemifacial microsomia (right side involved in over 60%)
- Microphthalmia or anophthalmia, blepharoptosis, retinal abnormalities, upper eyelid coloboma, epibulbar tumours (dermoid, lipodermoid, dermis-like)
- Macrostomia, mandibular hypoplasia
- Unilateral ear deformity ranging from a mildly dysmorphic ear to anotia (over 65%), preauricular tags or sinuses (over 40%), external auditory canal atresia, deafness
- Defects of vertebrae and ribs (Klippel- Feil anomaly, hemivetebrae, spina bifida, etc.)
- Defects of CNS (encephalocele, hydrocephaly, Arnold- Chiari malformation, holoprosencephaly, hypoplasia of corpus callosum etc.), heart (Ventricular Septal Defects, Tetralogy of Fallot, transposition of great vessels, etc.), kidney (renal aplasia, crossed renal ecopia, double ureter, etc.) trachea and lung (trachea- esophageal fistula, pulmonary hypoplasia/ aplasia), gastrointestinal system (imperforate anus, situs inversus)
- Defects of extremities (talipes equinovarus, radial ray deficiency)

Incidence:

The incidence of Goldenhar syndrome has been reported to be 1:3500-1:5600 with a male to female ratio of 3:2 (Vinay et. al., 2009). Right side is more affected than left with the ratio of 3:2

Genetics: Gene map locus 14q32

There is very little evidence to explain why Goldenhar Syndrome occurs. In most cases, Goldenhar Syndrome appears to occur randomly.

However, in some cases, positive family histories have been present that have suggested autosomal dominant or recessive inheritance. .Some studies show a gene map locus 14q32. In addition, some researchers suggest that the disorder may be caused by the interaction of many genes, possibly in combination with environmental factors i.e. multifactorial inheritance.

Diagnosis:

The diagnosis of Goldenhar syndrome may be complicated by the lack of any established diagnostic criteria, although ear anomalies are generally an essential component of the diagnosis.
In fact, some clinicians consider microtia to be a minimal manifestation of Goldenhar syndrome, and some diagnoses may be made based on isolated microtia alone (Araneta et al., 1997; Llano-Rivas, González-del Angel, del Castillo, Reyes, & Carnevale, 1999).

Differential Diagnosis:

Treacher Collins syndrome, Romberg syndrome (hemifacial atrophy) seen later in life could have a similar appearance to hemifacial microsomia, Craniosynostosis, Hemifacial microsomia.

References:

1. Araneta, M., Moore, C., Olney, R., Edmonds, L., Karcher, J., McDonough, C., et al. (1997). Goldenhar syndrome among infants born in military hospitals to Gulf War veterans.

2. Llano-Rivas, I., González-del Angel, A., del Castillo, V., Reyes, R., & Carnevale, A. (1999).Microtia: a clinical and genetic study at the National Institute of Pediatrics in Mexico. City. Arch Med Res, 30(2), 120-124.

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11. Kearns-Sayre syndrome

Kearns–Sayre Syndrome (KSS), also known as oculocraniosomatic disease or Oculocraniosomatic neuromuscular disease with ragged red fibres, is a mitochondrial myopathy with a typical onset before 20 years of age.

Characteristics:

KSS is characterized by three main features:

- Typical onset before age 20 although may occur in infancy or adulthood
- Chronic progressive external ophthalmoplegia (CPEO)
- Degeneration of the retina causing pigmentary retinopathy.
- In addition, one or more of the following conditions is present:
- Cardiac conduction defects
- Elevated cerebrospinal fluid protein
- Ataxia

Patients with KSS may also have such problems as deafness, dementia, kidney dysfunction, hypoparathyroidism and muscle weakness. Endocrine abnormalities including growth retardation, short stature, or diabetes may also be evident.

The first sign of this syndrome is ptosis, and after several years chronic progressive ophthalmoplegia may occur. Other presentations include atypical retinal pigment changes (salt and pepper like appearance) on fundus examination and high concentration of mitochondria in the extraocular muscles. Occasionally, incomitant strabismus, complete heart block, neurologic and endocrinologic symptoms may occur.

Prevalence:

It is a rare genetic disorder

Genetics:

In most cases KSS and CPEO is due to spontaneous deletions of the mitochondrial DNA (mtDNA) of up to 50% of the genome, which is believed to occur in the oocyte or during embryogenesis. The disorders can also be caused by mtDNA duplications that are maternally inherited. The clinical phenotype associated with mtDNA duplications are indistinguishable from those related to deletions.

These types of molecular rearrangements lead to defects in mitochondrial respiratory chain enzymes (complexes I, II, and IV) and energy metabolism.

The mtDNA with deletions is found in all tissues of the body. The percentage of deleted mtDNA molecules increases with age, possibly explaining the progressive nature of the condition.

Diagnosis:

The diagnosis is suggested by the clinical picture and by the presence of typical morphological alterations in the skeletal muscle (fibres presenting with mitochondrial proliferation or 'Ragged Red Fibres' and cytochrome c oxydase deficient fibres). It can be confirmed by the detection of high proportion of deleted mitochondrial DNA in a clinically or morphologically affected tissue (usually in the skeletal muscle).

Differential Diagnosis:

Ataxia with identified genetic and biochemical defects, Chronic Progressive External Ophthalmoplegia, failure to thrive, MELAS Syndrome, Myasthenia Gravis, Pearson Syndrome, Retinitis Pigmentosa, Sensorineural hearing loss

References:

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3. www.ninds.nih.gov/disorders/kearns_sayre/kearns_sayre.htm
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7. www.medterms.com/script/main/art.asp?articlekey=30811
8. Kearns –Sayre Syndrome Information: provided by the united mitochondrial disease foundation

12. Marshall Syndrome

Marshall syndrome is a very rare genetic disorder with an autosomal dominant pattern that equally affects males and females. It is caused by an abnormality in collagen, which is a key part of connective tissue.

Characteristics:

Marshall syndrome is characterised by mid-facial hypoplasia, sensorineural deafness and ocular defects (cataract, high myopia), a short nose, anteverted nostrils, and flat malar bones. Other abnormalities include ectodermal dysplasia, absent frontal sinuses, falx, tentorial and meningeal calcifications, spondyloepiphyseal abnormalities including slightly small and irregular distal femoral and proximal tibial epiphyses and wide tufts of distal phalanges. Occasional abnormalities include mental deficiency, retinal detachment and cleft palate.

Myopia, cataracts and glaucoma are common in Marshall syndrome. Moderate to severe hearing loss is often preceded by many incidents of otitis media (middle ear infection) and can occur in children as young as age three. Some patients also have osteoarthritis, particularly of the knees.

Prevalence:

Because of the rarity of this syndrome, very little demographic data is available.

Genetics:

The gene name for Marshall syndrome is Collagen, Type XI, alpha 1. The gene symbol is COL11A1. The chromosomal location is 1p21. Marshall syndrome is an autosomal dominant genetic trait and the risk of an affected parent transmitting the gene to the child is 50%.

Diagnosis:

Individuals are diagnosed by their features as well as by the very early onset of serious eye and eardisorder. Because Marshall syndrome is an autosomal dominant hereditary disorder, physicians can also note the characteristic appearance of the biological parent of the child. Genetic testing is costly, thus, it is not ordered for most people. As a result, people may be diagnosed as possible Marshall syndrome or possible Stickler syndrome, based on their symptoms and appearance.

Differential Diagnosis: Stickler syndrome, Spondyloepiphyseal Dysplasia Congenita (SED Congenita), Congenital Syphillis, Wagner syndrome.

References:

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8. www.whonamedit.com/synd.cfm/1665.html

13. NF2 - Bilateral Acoustic Neurofibromatosis *(Central Type Neurofibromatosis, Bilateral Acoustic Schwannomas, Bilateral Acoustic Neurofibromatosis; Bilateral Acoustic Neuroma,)*

Neurofibromatosis type 2 (NF2) is an autosomal-dominant inherited tumour predisposition syndrome caused by mutations in the NF2 gene on chromosome 22. It is characterised by the development of multiple schwannomas and meningiomas.

Characteristics:

The hallmark of NF2 is the bilateral occurrence of vestibular schwannomas (formerly called acoustic neuromas), benign, slow-growing tumours located on the vestibular branch of the eighth cranial nerve. However, other tumours, particularly meningiomas, spinal schwannomas, and ependymomas, are also frequent. The same tumour types that occur as multiple growths within an NF2 patient also occur as sporadic solitary tumours in the general population. Persons with the NF2 defect generally develop symptoms of eighth nerve dysfunction, including deafness and balance disorder, in early adulthood. In exceptional cases, onset occurs in childhood or is delayed until the fifth or sixth decade. The tumours of NF2 are histologically benign, but their anatomic locations make treatment difficult.

The majority of patients present with hearing loss, which is usually unilateral at onset and may be accompanied or preceded by tinnitus. Vestibular schwannomas may also cause dizziness or imbalance as a first symptom. Nausea, vomiting or true vertigo is rare symptoms, except in late-stage condition. The other main tumours are schwannomas of the other cranial, spinal and peripheral nerves; meningiomas both intracranial (including optic nerve meningiomas) and intraspinal, and some low-grade central nervous system malignancies (ependymomas). Ophthalmic features are also prominent and include reduced visual acuity and cataract. About 70% of NF2 patients have skin tumours (intracutaneous plaque-like lesions or more deep-seated subcutaneous nodular tumours).

Prevalence:

1 in 50,000 people without regard to sex or race (Olschwang , 2002)

Genetics:

22q12.2 (Autosomal dominant disorder localised to chromosome 22(long arm)).

Neurofibromatosis type 2 is a dominantly inherited tumour predisposition syndrome caused by mutations in the NF2 gene on chromosome 22. More than 50% of patients represent new mutations and as many as one-third is mosaic for the underlying disorder-causing mutation. Although truncating

mutations (nonsense and frameshifts) are the most frequent germline event and cause the most severe disease, single and multiple exon deletions are common.

Diagnosis:

Nf2 can be diagnosed with 65% accuracy prenatally with chorionic villus sampling or amniocentesis. The Manchester (modified NIH) diagnostic criteria for NF2 is given below. The original NIH criteria have been expanded to include patients with no family history who have multiple schwannomas and or meningiomas, but who have not yet developed bilateral 8th nerve tumours (Evans, 2009)

Main Criteria

- Bilateral vestibular schwannomas (VS)

  OR

- Family history of NF2 plus

  1) Unilateral VS or
  2) Any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities

Additional Criteria

- Unilateral VS plus any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities

  OR

- Multiple meningioma (two or more) plus unilateral VS or any two of: glioma, neurofibroma, schwannoma, and cataract
-

Differential Diagnosis: Neurofibromatosis 1, meningiomas, schwannomatosis

References:

1. Evans , D.G., Huson, S., Donnai, D., Neary, W., Blair, V., Newton, V., Harris, R.(1992) A clinical study of type 2 neurofibromatosis. Q J Med, 84:603-618.

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14. Norrie syndrome *(Atrophia Bulborum Hereditaria, Pseudoglioma, Episkopi Blindness,)*

Norrie's syndrome, a congenital progressive oculo-acoustico-cerebral degenerative condition, is a sex linked recessive disorder. Previously described as atrophia oculi congeneti, it is associated with bilateral pseudotumour of the retina, lens, and corneal opacities, and phthisis bulbi. Some patients develop progressive deterioration of mental function and hearing.

Characteristics:

Norrie's syndrome is an X-linked recessive condition of bilateral ocular malformation and blindness. During the first weeks of life, bilateral leucocoria (a condition where pupils appear white when light is shown on them) appears as a result of a whitish or yellowish mass of immature retina (pseudoglioma) behind the lens, on which a few vessels and elongated ciliary processes can be seen. The anterior chamber may be narrow. . During the first few months of life, the lenses develop cataracts and the corneas progressively opaque. Ocular pathology includes haemorrhage, vitreous opacities, glaucoma, iris atrophy, and synechiae (iris adheres to either cornea or lens). Phthisis bulbi (atrophy of the eye ball) is present by the end of the first decade. About one third of individuals with Norrie syndrome develop progressive sensorineural hearing loss between the ages of 20 and 30 years. Psychomotor retardation is frequent (65%), along with many systemic abnormalities (cardiac, pulmonary, skeletal, genitourinary, and gastrointestinal).

Prevalence:

The incidence and prevalence rates of the disorder are unknown.

Genetics:

Norrie syndrome is a genetic disorder caused by mutations in the NDP gene, located on Xp11.4 (GeneID: 4693). It is inherited in an X-linked recessive way.

Diagnosis:

The diagnosis is established by the finding of congenital pseudoglioma in a male infant with either typical systemic features or a family history of congenital blindness in male relatives.

Differential Diagnosis:

Retinoblastoma, recessively inherited retinal dysplasia, familial exudative retinopathy, retinopathy of prematurity, toxoplasmosis, Coat's disorder, retinal hamartomas and persistent hyperplastic primary vitreous

References:

1. Goodyear, H. M., Sonksen,P.M., and Mcconachie, H. (1989) Norrie's disease: a prospective study of development. Archives of Disease in Childhood, 64, 1587-1592.
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15. Pfeiffer Syndrome *(Acrocephalosyndactyly, Type V (ACS V); Noack Syndrome)*

Pfeiffer syndrome is a rare autosomal dominant inherited disorder that associates craniosynostosis, broad thumb and big toe, and partial syndactyly (webbed fingers and toes) on hands and feet. The patient with Pfeiffer's syndrome has a similar craniofacial deformity to that of the patients with Apert's and Crouzon syndromes. However, the midface in Pfeiffer's syndrome patients is usually more severely affected.

Characteristics:
Patients have premature fusion of the coronal and lambdoid sutures and occasionally of the sagittal sutures. There is a characteristic facial appearance:

- Disproportionally wide head with flat occiput
- Midfacial hypoplasia
- Ocular hypertelorism (widely spaced eyes) and ocular proptosis (prominence of the eyes)
- A small nose with low nasal bridge
- Dental problems are also common

Many of the characteristic facial features of Pfeiffer syndrome result from the premature fusion of the skull bones. The head is unable to grow normally, which leads to bulging and wide-set eyes, an underdeveloped upper jaw, and a beaked nose. About 50 percent of children with Pfeiffer syndrome have hearing loss (hearing loss with craniofacial syndromes), and dental problems are also common. Additionally, the thumbs and big toes are broader than normal and bend away from the other digits. Unusually short fingers and toes (brachydactyly) are also common, and there may be some syndactyly between the third and fourth digits.

Pfeiffer syndrome is divided into three subtypes. Type 1 or "classic" Pfeiffer syndrome has symptoms as described above. Most individuals with type 1 have normal intelligence and a normal life span. Types 2 and 3 are more severe forms of Pfeiffer syndrome, often involving problems with the nervous system. Type 2 consists of cloverleaf skull, extreme proptosis causing severe visual impairments, finger and toe abnormalities, developmental delay and neurological complications. Type 3 is similar to type 2, without the cloverleaf skull.

Prevalence:
Pfeiffer syndrome affects about 1 in 100,000 individuals (Vogels and Fryns, 2005).

Genetics:
Autosomal dominant inheritance. Mutations in the fibroblast growth factor receptor (FGFR) genes cause Pfeiffer syndrome: FGFR 1 (on chromosome 8p11.2-11) and FGFR 2 (on chromosome 10q26). Type 1 is caused by mutations in either the FGFR1 or FGFR2 gene. Types 2 and 3 are caused by mutations in the FGFR2 gene.

Diagnosis: Diagnosis is based on the presence of craniosynostosis and abnormal thumb and/ or first toe. Genetic investigations can be done to confirm the diagnosis.

Differential diagnosis: Apert syndrome, Carpenter syndrome, Crouzon syndrome, isolated cloverleaf skull, and Thanatophoric dysplasia

References:

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2. www.faces-cranio.org/Disord/Pfeiffer.htm
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6. http://www.skullbaseinstitute.com/pfeiffers.htm
7. www.thecraniofacialcenter.org/pfeiffer.html

16. Stickler syndrome *(Stickler Syndrome, Vitreous Type 1; Stickler Syndrome, Membranous Vitreous Type; Arthroophthalmopathy, Hereditary Progressive; AOM)*

Stickler syndrome, also known as hereditary progressive arthro-ophthalmopathy, is a genetically heterogeneous connective tissue disorder affecting the ocular, orofacial, and skeletal systems.

Characteristics:

The major systems involved in Stickler syndrome are the ocular, auditory, orofacial, and musculoskeletal systems. Severe myopia with onset in the first decade of life, vitreous degeneration, spontaneous retinal detachment, chorioretinal degeneration, open angle glaucoma, and presenile cataracts are the ocular features of the disorder. During early childhood, midface hypoplasia is often evident and becomes less pronounced with age in persons with COL2A1 mutations. Pierre Robin sequence bifid uvula, and/or cleft palate may be present and result in feeding and respiratory problems. Mixed and sensorineural hearing loss in the higher frequencies is also a feature of the syndrome. In early life, joint pain and stiffness may signify the onset of juvenile osteoarthritis. Early-onset degenerative joint disorder is a major complication in adulthood.

Prevalence:

The prevalence of stickler syndrome is 13.5 per 100,000 live births.(Orphanet report series, 2011)

Genetics:

Stickler syndrome is an autosomal dominant disorder caused by mutations in the COL2A1, COL11A1, or COL11A2 genes. Gene map locus is 12q13.11-q13.2.

Diagnosis:

Liberfarb et al. (2003) proposed a point system for establishing the diagnosis of Stickler syndrome. Two points are awarded for the presence of each of the following findings: cleft palate, vitreous degeneration or retinal detachment, and high-frequency sensorineural hearing loss. One point each is awarded for the characteristic facies, hypermobile tympanic membranes, a history of femoral head failure (severe delay in ossification), radiographically demonstrated osteoarthritis before age 40 years, spinal deformities, positive family history, and identification of a causative mutation. A score of 5 is necessary to make the diagnosis of Stickler syndrome.

Differential diagnosis: Marshall syndrome, Wagner syndrome, Marfan syndrome, Ehlers- Danlos syndrome, Reiters Syndrome, Ankylosing spondylitis

Stickler Syndrome and Marshall Syndrome

Marshall syndrome and Stickler syndrome closely resemble each other; in fact they are so similar, some say they are the same. The hearing loss associated with Stickler Syndrome can be progressive and usually involves the high frequencies. Sensorineural hearing loss has been reported in as many as 100% and as low as 20% of affected individuals. A conductive loss due to otitis can magnify an existing sensorineural loss and is a frequent problem for children with Marshall Syndrome. Ayme and Preus (1984) concluded, therefore, that there is 'no objective reason to consider that these two syndromes are not separate dominant disorders with variable expressivity.' They suggested that the facies differ. Patients with the Marshall syndrome have a flat or retracted midface whereas those with the Stickler syndrome have a flat malar region which is often erroneously described as a flat midface. Marshall Syndrome patients have a thick calvaria, abnormal frontal sinuses, and intracranial calcifications. The eyeballs appear large, possibly because of a shallow orbit.

References:

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2. Francomano, C.A. (2010) Stickler Syndrome. Management of Genetic Syndromes, Third Edition, Edited by Suzanne B. Cassidy and Judith E. Allanson. Copyright John Wiley & Sons, Inc.
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17. Sturge Weber Syndrome

Sturge Weber Syndrome also called as encephalofacial or encephalotrigeminal angiomatosis is a rare sporadically occurring neurocutaneous syndrome characterised by facial port wine stain in the trigeminal nerve distribution, glaucoma and vascular lesions in the ipsilateral brain and meninges.

Characteristics:

In its classical form the syndrome is characterized by

(1) a congenital, usually unilateral, capillary naevus ('port-wine stain') affecting the face, particularly the supraorbital region, often associated with buphthalmos or glaucoma;
(2) convulsions, usually contralateral to the side of the naevus;
(3) typical intracranial calcification, becoming radiologically visible after infancy;
(4) some degree of mental subnormality in the majority of the patients; and
(5) hemiparesis and homonymous hemianopia contralateral to the brain lesion

Atypical cases not displaying all features are well known. The radiological hallmark of the syndrome is double-contoured curvilinear calcification following a gyral pattern (Alexander and Norman, 1960), becoming radiologically recognizable later in childhood and involving most frequently the occipital and parietal area. This classical pattern seems to be pathognomonic for Sturge-Weber syndrome.

Prevalence:

Sturge – Weber syndrome occurs with a frequency of approximately 1 per 50,000 live births. (Thomas-Sohl et al, 2004)

Pathophysiology:

Angiomas of Sturge Weber syndrome result due to failure of regression of a vascular plexus around cephalic portion of neural tube which is destined to become facial skin. This vascular plexus normally forms at 6th week of intrauterine life and regresses by the 9th week. Failure of this regression results in residual vascular tissue which forms angiomas of leptomeninges, face and ipsilateral eye. These blood vessels show abnormal blood flow pattern as vasomotor phenomenon, venous occlusion, thrombosis and “vascular steal” phenomenon resulting in ischaemia, gliosis, atrophy and calcification of underlying cortical tissue. Although the leptomeningeal angioma in Sturge Weber syndrome is typically a static lesion, it has been demonstrated by some to be of progressive nature.

Diagnosis:

The diagnosis of Sturge- Weber syndrome is based on imaging studies, although CSF analysis may reveal elevated protein due to microhaemorrhages. Skull films may reveal tram track calcification caused by calcification in apposing gyri, ipsilateral calvarial thickening and enlargement of the paranasal sinuses and mastoid. Cranial CT demonstrates abnormal contrast enhancement of angioma, enlarged choroid plexus ipsilateral to the angioma and abnormal draining medullary and subependymal veins. Cortical atrophy underlying the angioma with gyri form “tram track” calcification is the characteristic imaging feature. Calcification however is unusual before 2 years of age and most commonly involves the parietal and occipital lobes. MRI is the current gold standard for diagnosis of disease which is reliable even in very young infants.

Differential Diagnosis:

Klippel-Trenaunay-Weber syndrome, Beckwith-Wiedemann syndrome, Dyke-Davidoff-Masson syndrome, Siderosis Calcification secondary to intrathecal methotrexate therapy and meningitis

References:

1. Boltshauser, E., Wilson, J., and Hoare, R. D. (1976) Sturge Weber syndrome with bilateral intracranial calcification. Journal of Neurology, neurosurgery and Psychiatry, 39, 429-35.

2. Thomas-Sohl, K.A., Vaslow, D.F., and Maria, B.L. (2004) Sturge-Weber syndrome: a review. Pediatr Neurol., 30(5):303-10.

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18.Treacher Collins syndrome *(Franceschetti-Zwahlen-Klein Syndrome; Mandibulofacial Dysostosis)*

Treacher Collins syndrome is an autosomal dominant disorder of craniofacial development.

Characteristics:

Treacher Collins syndrome is characterized by downward slanting palpebral fissures and hypoplasia of the zygomatic arches. Other craniofacial alterations of the syndrome are mandibular hypoplasia, coloboma, total or partial absence of lower eyelashes, accessory skin tags or blind pits between the tragus and the mandibular angle, external ear malformations, hearing loss, and malformations of the heart, kidneys, vertebral column and extremities. The oral manifestations are characterized by cleft palate, shortened soft palate, malocclusion, anterior open bite, and enamel hypoplasia.

Prevalence:

Prevalence of Treacher Collins syndrome is in the range 1 in 25,000 to 1 in 50,000 live births (Dixon, 1995).

Genetics:

The syndrome is caused by mutations in the TCOF1 gene (5q32-q33.1) encoding the nucleolar phosphoprotein treacle. Transmission is autosomal dominant with 90% penetrance and variable expressivity, even among affected patients within the same family.

Diagnosis:

Diagnosis is based on clinical findings and complementary examinations. Molecular tests confirm the diagnosis.

Differential Diagnosis: Goldenhar syndrome, Hemifacial microsomia, Nager syndrome, Miller syndrome.

References:

1. Dixon M. J. Treacher Collins syndrome. Jpurnal of Medical Genetics. 1995;32:806-808
2. Martelli-Junior H., Coletta R. D., Miranda R, de Barros L., Swerts M., Bonan P. Orofacial features of Treacher Collins syndrome. Med Oral Patol Oral Cir Bucal. 2009 July 1;14 (7):E344-8.
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19. Trisomy 13 (Trisomy 13-15, Patau syndrome)

Trisomy 13 or D1 trisomy or Patau syndrome is a clinically severe condition first described by Patau et al. (1960). It is a chromosomal anomaly caused by the presence of an extra chromosome 13 and is characterized by brain malformations (holoprosencephaly), facial dysmorphism, ocular anomalies, postaxial polydactyly, visceral malformations (cardiopathy) and severe psychomotor retardation. Eighty-two percent of the patients die within one month. Eighty-five percent do not survive beyond one year of life and most die before completing six months.

Characteristics:

The Patau syndrome phenotype typically includes severe central nervous system malformations, such as holoprosencephaly and arhinencephaly, with consequent severe psychomotor dysfunction and convulsions. This trisomy is characterized by the following triad: microphthalmia, cleft lip and palate and polydactyly. The face may also be characterized by prominent glabellae, ocular hypertelorism, anophthalmia, and micrognathia. The clinical features can be summarised as follows

- Growth retardation.
- Holoprosencephaly (60–70%).
- Microphthalmia/anophthalmia (60–70%).
- Cutis aplasia (scalp defects).
- Cleft lip/palate (60–70%).
- Cardiac malformations (80%), e.g. atrial septal defect (ASD) or ventricular septal defect (VSD).
- Postaxial polydactyly (60–70%) and/or limb reduction defects (occasional).
- Omphalocele.
- Kidney malformations.
- Severe/profound mental retardation.
- Ears are abnormally shaped and unusually low-set.

Prevalence:

Prevalence of Trisomy 13 is 1 in 5000 live births (Jones, 1998). It is the third most frequent trisomy among live births. Most embryos with trisomy 13 do not survive gestation and are spontaneously aborted. Of those surviving to term gestation, approximately 82-85% do not survive past 1 month of

age (Best, 2002), and 85% do not survive past 1 year of age and most die before completing six months (Widerемann et al., 1980). The sex ratio at birth is skewed toward females, presumably because of decreased survival among males, with continued skewing of the ratio further toward females as these children age (Best, 2002). Of those infants that survive past 1 year, most have few major malformations, but the prognosis remains poor, owing to multiple factors including long term neurological disability, feeding difficulty, and frequent pneumonia and other respiratory infections

Genetics: Extra Chromosome 13

Free trisomy 13 is found in around 75% of cases. In 20% of cases, trisomy 13 is associated with a Robertsonian translocation in which the supernumerary chromosome 13 becomes attached to another acrocentric chromosome (chromosomes 13, 14, 15, 21 or 22). In rare cases, the syndrome is caused by reciprocal translocation between chromosome 13 and a nonacrocentric chromosome. Mosaic trisomy 13 (in which there is both trisomic and normal cell types) has been reported in a few patients with a clinical picture that varies between a normal phenotype and that of classical trisomy 13 according to the number of trisomic cells present in the tissues. The risk of recurrence of trisomy (21, 13 or 18) in families of an index case with trisomy 13 is around 1%. However, in families in which trisomy 13 is associated with translocation (Robertsonian or balanced) the risk of recurrence is higher if one of the parents is a carrier of a balanced translocation.

Diagnosis:

Prenatal diagnosis is possible by chorionic villus sampling (CVS) at 11 weeks gestation or amniocentesis at 15 weeks gestation. Because of the high incidence of structural malformations in trisomy 13, there is a high detection rate (90%) on foetal anomaly USS.

Differential diagnosis: Smith-Lemli-Opitz syndrome (SLOS), Trisomy 18

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20. Trisomy 18 (Edward Syndrome)

Trisomy 18 (Edwards's syndrome) is second only to Trisomy 21 (Down's syndrome) as the most frequently occurring autosomal trisomy in neonates. Estimates of its frequency range from one in 3500 births to one in 14000 births. Female infants are 3 times more likely to have this trisomy than males. Affected infants are often born to women of advanced maternal age, and have a limited capacity for survival. 50% of these patients die within 2 months of birth, and only one in 10 survives the first year of life.

Characteristics:

Edward syndrome is characterized by growth delay, dolichocephaly, a characteristic facies, limb anomalies and visceral malformations. Hypotonia, hyporeactivity and feeding problems (poor suction) are present in the first weeks of life and are followed by a progression to hypertonia with infants showing an apparent lack of awareness of their surroundings. Common features are intrauterine and postnatal growth delay, an emaciated appearance with hypotrophy, microcephaly with a narrow skull and dolichocephaly, microretrognathia, hypertelorism, and poorly modelled and angular ears. Foot anomalies include pes equinovarus and/or rocker-bottom feet and the fingers overlap (the fifth and second fingers with the fourth and third). Malformations are common with involvement of the eyes (microphthalmia, coloboma), heart (over 90% of cases) digestive tract (esophageal atresia, anorectal malformations), kidneys and urinary tract (hydronephrosis, uni- or bilateral agenesis). Less frequently, cleft/lip palate, arthrogryposis, radial aplasia, spina bifida and anencephaly, holoprosencephaly and omphalocele are observed.

Prevalence:

Trisomy 18 is the second most common autosomal trisomy and has a quoted incidence of between 1 in 3000 and 1 in 8000(Young et.al., 1986; Carter et. al., 1985; Root and Carey, 1994) There is a female preponderence in this condition with a ratio of female to male being 3:1 caused in large part by a greater male fatality rate during the first few weeks of life (Weber, 1967).

Genetics:

The majority of cases are associated with free trisomy 18 resulting from nondisjunction. The extra chromosome 18 is of maternal origin in 90-97% of the cases and of paternal origin in 3-10 percent of the cases.

Among trisomy 18 cases of maternal origin, 31-39% results from nondisjunction in first meotic stage (MI) and 61-69% result from nondisjunction in second meotic stage (MII). Mosaic trisomy 18 has been detected in a few patients presenting with a clinical picture that varies from classical trisomy 18 to a normal phenotype depending on the number of trisomic cells present in the tissues. The trisomy 18 phenotype appears to be associated with the presence of three copies of the 18q11-q12 interval. The risk of recurrence of trisomy (21, 13 or 18) in families of an index case with trisomy 18 is around 1%. However, in families in which trisomy 18 is caused by translocation, the recurrence risk is higher if one of the parents is a carrier of a balanced translocation.

Diagnosis:

Trisomy 18 may be suspected during pregnancy from ultrasound findings (growth retardation, malformations, and multiple choroid plexus cysts) and can be confirmed by karyotype analysis of the foetus. Serum markers (used for the diagnosis of trisomy 21) may also be abnormal.

Differential Diagnosis: Trisomy 13, Arthrogryposis

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21. Turner Syndrome *(Ullrich-Turner syndrome; 45, X syndrome; 45,X/46 XX syndrome; Monosomy X)*

Turner syndrome is a chromosomal disorder associated with the complete or partial absence of an X chromosome. Individuals with this disorder have a female phenotype, but have abnormalities in reproductive function as well as a number of other clinical manifestations of disease.

Characteristics:

The presentation of Turner syndrome varies throughout a patient's life. Key clinical features of Turner syndrome are a lack of breast development or amenorrhea, with elevated follicle-stimulating hormone levels by 14 years of age; and infertility in women. Other characteristics of Turner syndrome include short stature, lymphoedema, a webbed neck, a low posterior hairline, misshapen or rotated ears, and a narrow palate with crowded teeth, a broad chest with widely spaced nipples, cubitus valgus, hyperconvex nails, multipigmented nevi, pubertal delay, and cardiac malformation

One third of patients with Turner syndrome have a cardiac malformation; 75 percent of these patients have coarctation of aorta or a bicuspid aortic valve. Progressive aortic root dilatation or dissection can also occur, particularly in patients with a bicuspid valve, coarctation, or untreated hypertension. Patients with Turner syndrome often have an atherogenic cardiovascular risk factor profile. Other potential complications of Turner syndrome include strabismus, sensorineural hearing loss, recurrent otitis media, orthodontic anomalies, renal malformation (e.g., horseshoe kidney, duplicated or cleft renal pelvis), autoimmune thyroiditis, celiac disorder, congenital hip dysplasia, and scoliosis.

Turner syndrome does not typically cause mental retardation or impair cognition. However, learning difficulties are common among women with Turner syndrome, particularly a specific difficulty in perceiving spatial relationships, such as nonverbal learning disorder. This may also manifest itself as a difficulty with motor control or with mathematics. While it is non-correctable, in most cases it does not cause difficulty in daily living. Most Turner Syndrome patients are employed as adults and lead productive lives.

There is also a rare variety of Turner Syndrome, known as "Ring-X Turner Syndrome", which has an approximate 60 percent association with mental retardation. This variety accounts for approximately 2–4% of all Turner Syndrome cases.

Common psychiatric problems include attention deficit disorder in elementary school age children and social adjustment problems in adolescence and early adulthood. Among those with moderate or severe learning difficulties, comorbidity with autism is common. Obsessive-compulsive symptoms are also common throughout childhood and adolescence, and clinical experience suggests they become more disabling in early adulthood.

Prevalence:

Overall the incidence of all abnormalities that include partial or complete monosomy X is between 1 in 2000 (Donaldson et.al., 2006) and 1 in 5000 (Sperling, 2008) live female births. Monosomy X is more frequent than structural anomalies among spontaneous abortions. It accounts for nearly 10% of all miscarriages and perhaps 1-2% of all human conceptions. As many as 99% of all 45,X foetuses do not survive to term, and most die by 28 weeks gestation. Unlike common human trisomies such as Down syndrome the risk of Turner syndrome does not increase with maternal (or paternal) age.

Genetics:

Most investigators believe that the phenotype in TS is the result of a deficiency of specific genes, most of which are as yet unidentified, rather than to the consequence of a single X chromosome (45, X) per se. One half of clinically identified cases possess part of a second X chromosome too, which is structurally abnormal, usually in association with some 45, X cells [Jacobs et al. 1997]. Most of the phenotypic features of TS are thought to be due to haploid (i.e. single and insufficient) dosage of these specific genes.

Because of X-inactivation, a random process occurring early in embryogenesis, only one X-chromosome is normally active during most of development. If a single X chromosome is associated with a phenotype (IS) this implies that in humans, X-inactivation is incomplete, and some essential gene products are transcribed from the 'silent' X chromosome too. They are needed in two expressed copies (i.e. diploid dosage) for normal development to take place. To maintain dosage equivalence in gene products between males and females, there are functionally equivalent genes on the Y chromosome too. SHOX, a gene that contributes to the short stature associated with the syndrome, lies in the pseudoautosomal region at the tip of the short arm of the X-chromosome, a region of homology with the Y chromosome in which pairing takes place during meiosis. No other 'Turner' gene has yet been discovered. Cytogenetically, there is great variation within the Turner population in terms of chromosomal constitution.

Approximately 50% have a single X-chromosome in all cells examined, of which most (70%) are maternal in origin. The great majority of the other 50% are mosaics, possessing at least two cell lines, one of which is 45, X. A small proportion has an additional normal 46, XX cell line (5%). In the remainder (40%) there is a second X which is structurally abnormal. In a few cases (6%), there is a structurally abnormal Y. The presence of a partial Y chromosome increases the risk of gonadoblastoma in situ, but how risk relates to the structure of that partial Y, or to specific Y linked genes, is as yet uncertain. There is a significantly increased risk of global learning difficulties and behavioural maladjustment in the nearly 30% of mosaic Turner subjects with a ring-X chromosome.

Diagnosis:

Turner syndrome may be diagnosed by amniocentesis during pregnancy. Sometimes, foetuses with Turner syndrome are identified by abnormal ultrasound findings (i.e. heart defect, kidney abnormality, cystic hygroma, and ascites). A standard 30 cell Karyotype is required for diagnosis of Turner syndrome, in order to exclude mosaicism. Diagnosis is confirmed by the presence of a 45, X cell line or a cell line with deletion of the short arm of the X chromosome (Xp deletion). A male phenotype excludes the diagnosis, regardless of karyotype.

Differential Diagnosis: Noonan syndrome, Constitutional delay of growth and development, 46,XX gonadal dysgenesis

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22. Usher syndrome

Usher syndrome (USH) is an autosomal recessive disorder comprising of bilateral sensorineural hearing loss, progressive loss of vision due to retinitis pigmentosa (RP), and variable vestibular dysfunction.

Characteristics:

Usher syndrome (US) is characterised by the association of sensorineural deafness (usually congenital) with retinitis pigmentosa (RP) and progressive vision loss. Some people with Usher syndrome also have vestibular dysfunction. Usher syndrome is the most common condition (aside from aging) that affects both hearing and vision. Three clinical entities have been defined:

Usher syndrome type 1 (USH1) – Patients with USH1 are congenitally affected with profound sensorineural hearing loss and absent vestibular function. This indicates defect in the nerve impulses generated in the vestibulum and cochlear hair cells, which affects development of walking and speaking as an early indication. These patients do not show subjective manifestations of RP at birth, although electroretinogram (ERG) is strongly altered and opthalmoscopy shows retinal pigmentary degenerations.

Usher syndrome type 2 (USH2) – USH2 is distinguished from USH1 with a less severe but still congenital hearing loss and preservation of vestibular function. The onset of RP overlaps with that of US1 and does not enable the differentiation between these two entities, although an ERG can be useful because only patients with USH2 present with a recordable a-wave (indicative of the generation of the nerve impulse).

Usher syndrome type 3 (USH3) – USH3 distinguishes from type 1 and 2 with a later onset of both hearing loss and RP. Deafness starts postlingually and is progressive, often diagnosed during the first decade and associated with vestibular disorders in half the cases. Progressive RP has its onset at the second decade of life and first manifests by visual discomfort at low light levels, followed by a gradual vision loss leading to total blindness within a few decades.

Prevalence: Epidemiological studies of USH show a prevalence of 3-6 patients per 100,000 inhabitants of the developed world (Boughman and Fishman, 1983; Forsius et al., 1971; Grondahl,

1987; Hope et al., 1997; Rosenberg et al., 1997; Spandau and Rohrschneider, 2002). Since false diagnosis of RP occurs frequently in infants, the prevalence is more likely to be 1/ 10,000 (Hope et al., 1997). The numbers of patients affected by the three distinct USH types is unequal. Studies in Europe show a proportion of 25- 44% of USH1 patients and 56- 75% of USH2 patients (Grondahl, 1987; Hope et al., 1997; Rosenberg et al., 1997; Spandau and Rohrschneider, 2002).

Genetics:

Transmission is autosomal recessive. With the advancement of the scientific methods, the genetic heterogeneity of the Usher syndrome was described toward the end of the 20th century. Using linkage analysis of patient families several independent loci on different chromosomes were identified (see table), in whom hereditary defects, which cause the Usher syndrome, were found. With the help of these loci the illness was divided in twelve subtypes (USH1A-G, USH2A-C, USH3A). Using interaction analysis techniques it could be shown that the identified gene products interact with one another in one or more larger protein complexes. If one of the components is missing, this protein complex cannot fulfil its function in the living cell and it probably comes to the degeneration the same. The function of this protein complex has been suggested to participate in the signal transduction or in the cell adhesion of sensory cell.

Known Usher syndrome subtypes (Reiners et al., 2006).

Usher-Type	Gene locus	Gene	Protein	Function
1A	14q32	HEMAP ?	EMAP	MAP(cytoskeleton)
1B	11q13.5	MYO7A	Myosin VIIA	Motor protein
1C	11p15.1-p14	USH1C	Harmonin	Scaffold protein
1D	10q21-q22	CDH23	Cadherin 23	Cell adhesion
1E	21q21			
1F	10q11.2-q21	PCDH15	Protocadherin 15	Cell adhesion
1G	17q24-q25	USH1G	SANS	Scaffold protein
2A	1q41	USH2A	Usherin	
2B	3p23-p24.2	SLC4A7	NBC-3	Cotransporter of ions
2C	5q14.3-q21.1	VLGR1	VLGR1b	Very large GPCR
3A	3q21-q25	USH3A	Clarin-1	
3B	20q			

Diagnosis:

Clinical diagnosis is based on findings of bilateral sensorineural hearing loss (symmetric, congenital and profound for type 1, and moderate to severe with a predominant sensorineural high-frequency loss for type 2) associated with retinitis pigmentosa (pigment deposits on fundoscopy and a flat or diminished electroretinogram). Genetic testing is feasible with preliminary linkage analysis followed by molecular diagnosis based on genomic sequencing of candidate genes.

Differential diagnosis: Alport syndrome, Alstrom syndrome, Bardet-Biedl syndrome, Cockayne syndrome, spondyloepiphyseal dysplasia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hurler syndrome (MPS-1), Kearns-Sayre syndrome (CPEO), Norrie syndrome, osteopetrosis (Albers-Schonberg disease),Refsum's disease (phytanic acid storage disease), and Zellweger syndrome (cerebro-hepato-renal syndrome).

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Glossary

ADAS: Autosomal Dominant Alport Syndrome
ARAS: Autosomal Recessive Alport Syndrome
AS: Alport Syndrome
BBS : Bardet Biedl syndrome
CdLS: Cornelia de Lange syndrome
CNS: Central Nervous System
CPEO: Chronic progressive external ophthalmoplegia
CRS: Congenital rubella syndrome
CSF: Cerebrospinal Fluid
ERG: Electro Retinogram
FGFR2: Fibroblast Growth Factor Receptor 2)
GBM: Glomerular Basement Membrane
IgM: Immunoglobulin M
LMBBS : Laurence Moon-Bardet-Biedl syndrome
NF2: Neurofibromatosis type 2
OAV Dysplasia: Oculoauriculovertebral Dysplasia
USH1: Usher Syndrome Type 1
USH2: Usher Syndrome Type 2
USH3: Usher Syndrome Type 3
XLAS: X-linked Alport Syndrome
Anophthalmia: Congenital absence of one or both eyes
Anotia: total absence of the auricle most often with narrowing or absence of the external auditory meatus
Apoptosis: Programmed cell death
Aphakic glaucoma: is glaucoma which develops in an aphakic eye (one which has had its lens removed).
Arhinencephaly: Anterior midline brain, cranial, and facial malformations resulting from the failure of the embryonic prosencephalon to undergo segmentation and cleavage. Also called as holoprocencephaly
Arnold- Chiari malformation: a malformation of the brain
Atresia choanae: back of the nasal passage (choana) is blocked, usually by abnormal bony or soft tissue formed during fetal development.

Blepharitis: inflammation of the eyelash follicles, along the edge of the eyelid
Blepharoptosis: drooping of the upper eyelid
Brachicephaly: broad, short head
Brachydactyly: unusually short fingers and toes
Buphthalmos: enlargement of the eyeball
Calvaria: skull cap. It is the upper part of the cranium and surrounds the cranial cavity containing the brain
Coloboma: a gap in part of the structures of the eye, caused when a baby's eyes do not develop properly during pregnancy
Cryptorchidism: Failure of one or both testes to descend into the scrotum
Cubitus valgus: a condition of the arm in which the forearm deviates away from the midline of the body when extended
Dolichocephaly: the condition where the head is disproportionately long and narrow.
Dysostosis: disorder of the development of bone, in particular affecting ossification
Dysplastic ears: abnormal shape and small size of the ears
Encephalocele: rare neural tube defect where brain membranes protrude through openings in the skull
Ependymomas: a tumor that forms in the tissues of the brain and spinal cord
Epicanthic folds: small skin folds on the inner corners of the eyes
Glioma: a type of tumor that starts in the brain or spine. It is called a glioma because it arises from glial cells.
Haematuria: presence of red blood cells (erythrocytes) in the urine
Hemianopia: loss of vision in either the whole left or the whole right half of the field of vision. Also called hemianopsia
Hemiparesis: weakness on one side of the body
Hirsutism: excessive hairiness on women in those parts of the body where terminal hair does not normally occur or is minimal
Holoprosencephaly: an incomplete or absent division of the embryonic forebrain (prosencephalon) into distinct lateral cerebral hemispheres. Also called as arhinencephaly
Hydrocephaly: a disturbance of formation, flow, or absorption of cerebrospinal fluid (CSF) that leads to an increase in volume occupied by this fluid in the CNS
Hypertelorism: widely spaced eyes
Hypoparathyroidism: an endocrine disorder in which the parathyroid glands in the neck do not produce enough parathyroid hormone

Hypoplasia: underdevelopment or incomplete development of a tissue or organ
Hypotonia: low muscle tone
Leiomyomatosis: occurrence of multiple leiomyomas (a benign tumor derived from smooth muscle) throughout the body
Lenticonus: bulging of the lens capsule and the underlying cortex of the eyes. Lenticonus anterior is part of the Alport syndrome
Macrostomia: greatly exaggerated width of the mouth
Macrothrombocytopenia: blood platelets are abnormally large
Meningiomas: a set of tumors that arise contiguously to the meninges, i.e. the covering of the brain and spinal cord
Microcephaly: circumference of the head is more than two standard deviations smaller than average for the person's age and sex
Micrognathia: a condition where the mandible (jaw) is undersized
Micromelia: abnormal shortness or smallness of limbs
Microphthalmia: small eye
Microretrognathia: Micrognathia is abnormally small mandible; retrognathia is abnormal posterior placement of the mandible
Microtia: the external portion of the ear (the auricle) is malformed. In the strictest definition, there is also narrowing or absence of the external auditory canal (external auditory meatus).
Nystagmus: periodic involuntary rhythmic ocular oscillation of the eyes
Oblique palpebral fissures: upward slant to the eyes
Omphalocele: a type of abdominal wall defect in which the intestines, liver, and occasionally otherorgans remain outside of the abdomen in a sac because of a defect in the development of the muscles of the abdominal wall
Ophthalmoplegia: paralysis or weakness of one or more of the muscles that control eye movement
Panencephalitis: encephalitis that affects both gray and white matter of the brain, resulting in progressive loss of mental and motor functions
Phthisis bulbi: atrophy of the eye ball
Polydactyly: a person has more than five fingers per hand or five toes per foot
Polydipsia: patient displays excessive thirst
Polyuria: excessive or abnormally large production and/or passage of urine
Proptosis: prominent eyeballs
Proteinuria: presence of an excess of serum proteins in the urine

Ptosis: drooping eyelid
Radial ray deficiency: underdevelopment or total loss of the radius bone in the forearm
Retinopathy: some form of non-inflammatory damage to the retina of the eye
Schwannomas: benign tumors of the Schwann cells (nerve sheath) that grow slowly and push nerve fibers aside.
Simian crease: single deep crease across the centre of the palm
Syndactyly: webbed or conjoined fingers
Synechiae: iris adheres to either cornea or lens
Synophrys: bushy eyebrows meeting the midline
Talipes equinovaris: Clubfoot, where the foot turns inward and downward

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11	The Clarke School For the Deaf and Mentally Retarded	Dr. P. Leelavathy Director	#3, 3rd Street, Dr. Radhakrishnan Road, Mylapore, Chennai - 600 004	(044) 28475422 (044) 28474910 clarkskn@md2.vsnl.net.in
12	Holy Cross Service Society	Prof. Dr. S. Prabakar Director	Plot No 3., Ettupattai Compound Puthur Tiruchirapally 620 017 Tamilnadu	(0431) 2771544 holy.cross.service.society @gmail.com
13	Cadre India	Mr. Mohanakumar E Director	Kurumathoor, Kuzhithurai PO Kanyakumari District Tamilnadu, India Pin – 629 163	(04651) 261211 cadreindia@gmail.com
14	Upahar Madurai	Mr. L. Shanmugam Secretary	37, Teachers Colony, 2nd Floor, Muthupatti, Alagappan Nagar, Madurai, 625 003 Tamilnadu	(0452) 2693666 upaharieic@gmail.com

15	National Institute for Empowerment of Persons with Multiple Disabilities (NIEPMD) (Government of India Ministry of Social Justice and Empowerment)	Dr. Neeradha Chandramohan Director	East Coast Road Muttukadu - 603112 Kancheepuram District, Tamil Nadu, India	(044) 27472389 niepmd@gmail.com
	MAHARASHTRA			
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18	National Association for the Blind - Department of Education	Mr. Raman Shanker Director Education	11, Khan Abdul Gaffar Khan Road, Worli Seaface, Mumbai-400 030	(022) 24935370 (022) 24935365 nabed@vsnl.com
19	Ali Yavar Jung National Institute for the Hearing Handicapped	Dr. R. Rangasayee Director	K.C.Marg, Bandra Reclamation, Bandra (W) Mumbai – 400 050	(022) 26422638 rangasayee2002@yahoo.co.in
20	Muskan Centre for Child Development	Ms. Dipti Gandhi Director - Founder Trustee	15, Prashanti,kalanagar, Opp MAHADA, Bandra (E). Mumbai Maharashtra	(022) 26592745 (022) 32174883 dipti_gandhi@hotmail.com
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21	National Association for the Blind – New Delhi	Mr. T. C. Alakh Hon. Gen. Secretary	Sector 5, R. K. Puram, New Delhi 110022	(011) 26102944 (011) 26175886 dbmhuprogam@gmail.com

22	National Trust Ministry of Social Justice and Empowerment	Ms. Poonam Natrajan Chairperson	16B, Bada Bazar Road, Old Rajinder Nagar New Delhi - 110060	(011) 43187878 contactus@thenationaltrust.in
23	Rehabilitation Council of India	Dr. J P Singh Member Secretary	Rehabilitation Council of India B-22, Qutab Institutional Area New Delhi - 110 016	(011) 26532816, 26534287 (011) 26532384,26532408 rehabstd@nde.vsnl.net.in
24	EdCIL –SSA	Dr Anupriya Chadha Consultant, Edcil, SSA	10-B, Indraprastha Estate New Delhi-110 002	anupriya82@yahoo.co.in
25	IGNOU-National Centre for Disability Studies	Dr. Hemlata Director	National Centre for Disability Studies, Indira Gandhi National Open University, Zakir Hussain Block (Ground Floor), Maidan Garhi, New Delhi - 110068 India	(011)29531574 (011) 29531575 (011) 29532124 n.c.d.s.2008@gmail.com
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32	Sharp Memorial School for the Blind	Mr. P.M. Samuel Superintendent	P.O. Rajpur, District Dehradun, Uttarakhand- 248009	sharpmemorial.1887@gmail.com
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33	Shikshit Yuva Sewa Samiti	Mr. Gopal Krishna Agarwal Director	Pandey bazar, Basti – 272002, Uttar Pradesh	(05542) 242280 syssbst@sify.com
34	Saksham Daksh	Ms. Bipasha Sen Gupta General Secretary	D-69, Sector 55, Noida 201301.	(011) 42411015 bipashasen2@rediffmail.com
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40	Madhya Pradesh Welfare Association for the Blind	Mr. M.V.Shirdhonakar President	33. B/D, Kila Maidan Insudtrial Area Indore-452 006	(0731) 2401242 mpwab@rediffmail.com
41	Digdarshika Institute of Rehabilitation and Research	Mr. Sumit Roy Executive Director	B 292, Shahpura, District - Bhopal Madhya Pradesh – 462016	(0755) 2460947 (0755) 2426923 dirr89@rediffmail.com
	JHARKHAND			
42	Nav Bharat Jagruti Kendra	Mr. Satish Girija President	At: Amritnagar, P.O.Korrah, Dist – Hazaribag – 825301 Jharkhand	(06546)263332 nbjkco@gmail.com, nbjkco2@rediffmail.com

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43	Society for the Visually Handicapped,	Dr. Ruma Chatterjee Vice President	12, Dover Road Kolkata -700019	(033) 24759581 (033) 24758865 ruma1@rokectmail.com
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SYNDROME	Alport syndrome	Alstrom syndrome	Apert syndrome	Bardet-Biedl syndrome	Cornelia de Lange Syndrome	Charge syndrome	Congenital Rubella Syndrome	Crouzon syndrome	Down syndrome (Trisomy 21)	Goldenhar syndrome	Kearns–Sayre syndrome
CHARACTERISTICS	**H**aematuria and Proteinuria **H**ypertension **R**enal impairment **S**ensory neural hearing loss **O**phthalmic lesions	**N**ystagmus **L**ight sensitivity **R**etinopathy and blindness **H**earing impairment **D**iabetes mellitus **D**evelopmental delay **O**besity **C**ardiomyopathy	**P**remature fusion of skull bones **F**ull length webbing between 2nd, 3rd and 4th fingers, as well as the toes **V**isual problems **H**earing loss **M**ild mental retardation **C**left palate	**R**etinal dystrophy, **O**besity, **P**olydactyly, **M**ale hypogonadism, **M**ental retardation, **R**enal dysfunction **N**eurological, speech, and language deficits, **A**uditory deficiency, **B**ehavioural traits, **F**acial dysmorphism, **D**ental anomalies	**D**elay in growth and development, hirsute, anomalies in the structure of the limbs and distinctive facial characteristics **O**cularly they may present palpebral ptosis, conjunctivitis or chronic blepharitis, stenosis of the palpebral canal, severe myopia, and nystagmus.	**O**cular Coloboma **C**hoanal atresia/stenosis **C**ranial nerve anomalies **C**haracteristic ear anomalies **C**ardiovascular malformations **G**enital hypoplasia **C**left lip/palate **T**racheoesophageal-fistula **D**istinctive CHARGE facies **G**rowth deficiency **D**evelopmental delay	Sensorineural deafness, various ocular abnormalities such as cataract, retinopathy or glaucoma; cardiovascular defects mild to severe mental retardation with microcephaly and spastic diplegia	Premature closure of the cranial sutures, midface hypoplasia, exophthalmia, proptosis, optical atrophy, conductive hearing loss	**M**uscle hypotonia; flat facial profile, including a somewhat depressed nasal bridge and small nose, oblique palpebral fissures, dysplastic ears, simian crease, joint hypermobility, fifth finger has one bending joint instead of two (dysplastic middle phalanx), epicanthal folds, excessive space between large and second toe (sandal gap); enlargement of tongue in relationship to size of mouth. **C**ongenital heart defects, gastroesophageal reflux disease, recurrent ear infections, obstructive sleep apnoea, and thyroid dysfunctions.	**F**acial asymmetry, hemifacial microsomia (right side involved in over 60%) **M**icrophthalmia or anophthalmia, blepharoptosis, retinal abnormalities, upper eyelid coloboma, epibulbar tumours (dermoid, lipodermoid, dermis-like) Macrostomia, mandibular hypoplasia **U**nilateral ear deformity ranging from a mildly dysmorphic ear to anotia (over 65%), preauricular tags or sinuses (over 40%), external auditory canal atresia, deafness Defects of vertebrae and ribs (Klippel- Feil anomaly, hemivetebrae, spina bifida, etc.) **D**efects of CNS (encephalocele, hydrocephaly, Arnold- Chiari malformation, holoprosencephaly, hypoplasia of corpus callosum etc.), **D**efects of heart (ventricular Septal Defects, Tetralogy of Fallot, transposition of great vessels, etc.), **D**efects of kidney (renal aplasia, crossed renal ecopia, double ureter, etc.) trachea and lung (trachea-esophageal fistula, pulmonary hypoplasia/ aplasia), **D**efects of gastrointestinal system (imperforate anus, situs inversus) Defects of extremities (talipes equinovarus, radial ray deficiency)	**T**ypical onset before age 20 although may occur in infancy or adulthood **C**hronic progressive external ophthalmoplegia (CPEO) **D**egeneration of the retina causing pigmentary retinopathy. **C**ardiac conduction defects **E**levated cerebrospinal fluid protein **A**taxia **D**eafness, dementia, kidney dysfunction, hypoparathyroidism and muscle weakness.
AETIOLOGY	**G**enetic XLAS (X-linked Alport Syndrome) **ARAS** (Autosomal Recessive Alport Syndrome) **ADAS** (Autosomal Dominant Alport Syndrome)	Autosomal recessive disorder caused by a mutation in a gene located on chromosome 2 (2p13).	Autosomal dominant; genetic mutation in the FGFR2 (fibroblast growth factor receptor 2) gene.	Autosomal recessive mutations in 14 genes are known to be associated with BBS	**A**utosomal dominant inheritance **NIPBL** and SMC1A (formerly SMC1L1) are the only genes currently known to be associated with CdLS.	**A**utosomal dominant inheritance **G**ene map locus 8q12.1, 7q21.1	Placental infection during maternal viraemia	**A**utosomal dominant pattern. **T**he mutation in the genes that codify receptor 2 of the (FGFR2) fibroblast growth factor is responsible for the deformities observed.	Trisomy 21	**I**diopathic in most cases **M**ultifactorial inheritance **G**ene map locus 14q32	**S**pontaneous deletions of the mitochondrial DNA (mtDNA) of up to 50% of the genome **C**an also be caused by mtDNA duplications that are maternally inherited.
DIFFERENTIAL DIAGNOSIS	**MYH9** disorders (Epstein's syndrome and Fechtner's syndrome), **B**ranchio-oto-renal syndrome, **T**hin basement membrane nephropathy, **M**aternally inherited diabetes and deafness	**B**ardet–Biedl syndrome (BBS), **L**eber congenital amaurosis (LCA), **I**diopathic cardiomyopathy in infants.	**C**rouzon syndrome, **P**feiffer Syndrome	**M**cKusick-Kaufman syndrome, **A**lstrom syndrome, **J**oubert syndrome, **S**enior-Loken syndrome, **L**eber congenital amaurosis, **B**iemond syndrome type II	Fetal Alcohol syndrome	**V**ACTERL association, **D**iGeorge sequence, **V**elocardiofacial syndrome (VCFS), Cat Eye Syndrome, retinoic acid embryopathy, and PAX2 abnormalities	Cytomegalovirus, toxoplasmosis, herpes simplex, varicella zoster	Apert Syndrome, Pfeiffer syndrome, Carpenter syndrome, Saethre-Chotzen syndrome	Trisomy 18, Multiple X chromosomes	**T**reacher Collins syndrome, Romberg disease (hemifacial atrophy) seen later in life could have a similar appearance to hemifacial microsomia, **C**raniosynostosis, Hemifacial microsomia.	**A**taxia with identified genetic and biochemical Defects, **C**hronic Progressive External Ophthalmoplegia, **F**ailure to Thrive, **M**ELAS Syndrome, **M**yasthenia Gravis, **P**earson Syndrome, **R**etinitis Pigmentosa, **S**ensorineural hearing loss

SYNDROME	Marshall Syndrome	Nf2 - Bilateral Acoustic Neurofibromatosis	Norrie's disease	Pfeiffer Syndrome	Stickler syndrome	Sturge Weber Syndrome	Treacher Collins syndrome	Trisomy 13 (Patau Syndrome)	Trisomy 18 (Edward Syndrome)	Turner syndrome	Usher syndrome
CHARACTERISTICS	**M**id-facial hypoplasia, sensorineural deafness and ocular defects (cataract, high myopia), a short nose, anteverted nostrils, and flat malar bones. **O**ther abnormalities include ectodermal dysplasia, absent frontal sinuses, falx, tentorial and meningeal calcifications, spondyloepiphyseal abnormalities including slightly small and irregular distal femoral and proximal tibial epiphyses and wide tufts of distal phalanges. **O**ccasional abnormalities include mental deficiency, retinal detachment and cleft palate	**B**ilateral occurrence of vestibular schwannomas **M**eningioma, glioma, neurofibroma, schwannoma, **P**osterior subcapsular opacities and cataract	**B**ilateral leucocoria Ocular pathology includes haemorrhage, vitreous opacities, glaucoma, iris atrophy, synechiae, and phthisis bulbi, **P**rogressive sensorineural hearing loss, psychomotor retardation, systemic abnormalities (cardiac, pulmonary, skeletal, genitourinary, and gastrointestinal).	**C**raniosynostosis, broad thumb and big toe, and partial syndactyly (webbed fingers and toes) on hands and feet. **D**isproportionally wide head with flat occiput **M**idfacial hypoplasia **O**cular hypertelorism (widely spaced eyes) and ocular proptosis (prominence of the eyes) **A** small nose with low nasal bridge **D**ental problems are also common	**S**evere myopia with onset in the first decade of life, vitreous degeneration, spontaneous retinal detachment, chorioretinal degeneration, open angle glaucoma, and presenile cataracts are the ocular features of the disorder. **M**idface hypoplasia is often evident and becomes less pronounced with age **P**ierre Robin sequence bifid uvula, and/or cleft palate may be present. **M**ixed and sensorineural hearing loss in the higher frequencies **I**n early life, joint pain and stiffness may signify the onset of juvenile osteoarthritis. **E**arly-onset degenerative joint disease is a major complication in adulthood.	**A** congenital, usually unilateral, capillary naevus ('port-wine stain') affecting the face, particularly the supraorbital region, often associated with buphthalmos or glaucoma; **C**onvulsions, usually contralateral to the side of the naevus; **T**ypical intracranial calcification, becoming radiologically visible after infancy; **S**ome degree of mental subnormality in the majority of the patients; and **H**emiparesis and homonymous hemianopia contralateral to the brain lesion	**D**ownward slanting palpebral fissures and hypoplasia of the zygomatic arches. **M**andibular hypoplasia, coloboma, total or partial absence of lower eyelashes, accessory skin tags or blind pits between the tragus and the mandibular angle, external ear malformations, hearing loss, and malformations of the heart, kidneys, vertebral column and extremities. **T**he oral manifestations are characterized by cleft palate, shortened soft palate, malocclusion, anterior open bite, and enamel hypoplasia.	**G**rowth retardation. Holoprosencephaly (60–70%). **M**icrophthalmia/anoph-thalmia (60–70%). **C**utis aplasia (scalp defects). **C**left lip/palate (60–70%). **C**ardiac malformations (80%), e.g. atrial septal defect (ASD) or ventricular septal defect (VSD). **P**ostaxial polydactyly (60–70%) and/or limb reduction defects (occasional). **O**mphalocele. **K**idney malformations. **S**evere/profound mental retardation. Ears are abnormally shaped and unusually low-set.	**H**ypotonia, hyporeactivity and feeding problems (poor suction) are present in the first weeks of life and are followed by a progression to hypertonia Intrauterine and postnatal growth delay, an emaciated appearance with hypotrophy, microcephaly with a narrow skull and dolichocephaly, microretrognathia, hypertelorism, and poorly modelled and angular ears. **F**oot anomalies include pes equinovarus and/or rocker-bottom feet and the fingers overlap (the fifth and second fingers with the fourth and third). **M**icrophthalmia, coloboma, esophageal atresia, anorectal malformations\hydronephrosis, uni- or bilateral agenesis. **C**left/lip palate, arthrogryposis, radial aplasia, spina bifida and anencephaly, holoprosencephaly and omphalocele	**L**ack of breast development or amenorrhea, with elevated follicle-stimulating hormone levels by 14 years of age; and infertility in women. **S**hort stature, lymphoedema, a webbed neck, a low posterior hairline, misshapen or rotated ears, and a narrow palate with crowded teeth, a broad chest with widely spaced nipples, cubitus valgus, hyperconvex nails, multipigmented nevi, pubertal delay, and cardiac malformation	Association of sensorineural deafness (usually congenital) with retinitis pigmentosa (RP) and progressive vision loss. Some people with Usher syndrome also have vestibular dysfunction
AETIOLOGY	**A**utosomal dominant genetic trait **G**ene: COL11A1 **C**hromosomal location is 1p21	**A**utosomal dominant disorder **G**ene map locus: 22q12.2	**X**- linked recessive inheritance **C**aused by mutations in the gene, located on Xp11.4	**A**utosomal dominant inheritance FGFR 1 (on chromosome 8p11.2-11) and FGFR 2 (on chromosome 10q26)	**A**utosomal dominant disorder caused by mutations in the COL2A1, COL11A1, or COL11A2 genes. **G**ene map locus is 12q13.11-q13.2	**F**ailure of regression of a vascular plexus around cephalic portion of neural tube which is destined to become facial skin.	**A**utosomal domianant inheritance. **C**aused by mutations in the TCOF1 gene (5q32-q33.1) encoding the nucleolar phosphoprotein treacle	**T**risomy 13	**T**risomy 18	45X	**A**utosomal recessive transmission **T**welve subtypes (USH1A-G, USH2A-C, USH3A)
DIFFERENTIAL DIAGNOSIS	**S**tickler syndrome, **S**pondyloepiphyseal Dysplasia **C**ongenita (SED Congenita), **C**ongenital Syphillis, Wagner syndrome	**N**eurofibromatosis 1, **M**eningiomas, **S**chwannomatosis	**R**etinoblastoma, recessively inherited retinal dysplasia, familial exudative retinopathy, retinopathy of prematurity, toxoplasmosis, Coat's disease, retinal hamartomas and persistent hyperplastic primary vitreous	**A**pert syndrome, **C**arpenter syndrome, **C**rouzon syndrome, isolated cloverleaf skull, and **T**hanatophoric dysplasia	**M**arshall syndrome, **W**agner syndrome, **M**arfan syndrome, **E**hlers- Danlos syndrome, **R**eiters Syndrome, **A**nkylosing spondylitis	**K**lippel-Trenaunay-Weber syndrome, **B**eckwith-Wiedemann syndrome, **D**yke-Davidoff-Masson syndrome, **S**iderosis Calcification secondary to intrathecal methotrexate therapy and meningitis	**G**oldenhar syndrome, **H**emifacial microsomia, **N**ager syndrome, **M**iller syndrome.	**S**mith-Lemli-Opitz syndrome (SLOS), **T**risomy 18	**T**risomy 13, **A**rthrogryposis	**N**oonan syndrome, **C**onstitutional delay of growth and development, 46,XX gonadal dysgenesis	**A**lport syndrome, **A**lstrom syndrome, **B**ardet-Biedl syndrome, **C**ockayne syndrome, **S**pondyloepiphyseal dysplasia congenita, **F**lynn-Aird syndrome, **F**riedreich ataxia, **H**urler syndrome (MPS-1), **K**earns-Sayre syndrome (CPEO), **N**orrie syndrome, **O**steopetrosis (Albers-Schonberg disease), **R**efsum's disease (phytanic acid storage disease), and (cerebro-hepato-renal syndrome).