genetic CLINICS

Newsletter of Genetics Chapter of Indian Academy of Pediatrics

Volume: 1
Issue: 2 (Oct.-Dec. 2008)

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Prenatal Diagnosis and Indian Law

Shubha Phadke

The first issue of Genetic Clinics got a very good response from clinicians in India and our well wisher geneticists from abroad. The timing of the beginning of the clinical genetics appears to be right for genetic scenario in India. I hope to get contributions of reports of postnatal or prenatal diagnosis of uncommon genetic disorders. This will help to spread the message of available diagnostic facilities in India and increase awareness about rare genetic disorders amongst clinicians.

Today, I wish to stress the message that though prenatal diagnosis is an important part of helping families with genetic disorders, it is NOT the only hope or option for the families with genetic disorders. Genetic diseases were being treated with good outcome long before the specialty of clinical genetics came into existence. The results of the treatment of Wilson disease, hemophilias and other bleeding disorders, congenital adrenal hyperplasia, hereditary spherocytosis, thalassemias, many metabolic disorders like galactosemia, phenylketonuria, etc, surgically treatable malformations are satisfactory. The various strategies of treatment include diet modifications, megadoses of vitamins, replacement of deficient protein, bone marrow transplantation and other organ replacement, drug therapy and surgical removal of defective organ. The success of newer treatments like enzyme replacement therapy is likely to be repeated in many more disorders. Though the gene therapy for all patients appears to be a distant dream, other genetic strategies like small interference RNA (si RNA) are showing a great promise for many genetic disorders. Identification of causative genes and modifier genes is improving the knowledge of pathogenesis of genetic disorders and this will lead to development of new drugs.

At the same time, identification of genes for monogenic disorders is progressing rapidly and, at present, genetic defects for more than 2000 phenotypes have been identified. It means that DNA based prenatal diagnosis is possible for these disorders. Scientists are working on microarray based analysis of amniotic fluid. This can screen all pregnancies for whole genome wide genetic imbalances. Availability of DNA based diagnosis of monogenic disorders is improving rapidly in India. Even if not available in India, DNA samples can be sent abroad and Indian patients can avail of all the latest prenatal diagnostic facilities. Greatly improved resolution of ultrasonography machines has added to prenatal diagnosis and major and many minor malformations can be easily diagnosed prenatally. The developments in the field of fetal therapy are also remarkable and successful treatment with medical and surgical modalities for fetal disorders is possible.

With this advanced scenario of genetic disorders and prenatal diagnosis in India and world over, many families at risk of genetic disorders are benefited. But like many other medical developments, research in genetics is posing many ethical dilemmas. This is especially true for prenatal diagnosis. Niketa's recent legal battle to terminate her pregnancy at 24 weeks for prenatal diagnosis of complete heart block in her baby brought this dilemma in every household. The situations of prenatal diagnosis of minor anomaly, treatable disorder, disorder with uncertain outcome and prenatal diagnosis of an anomaly in later part of pregnancy are not uncommon. These situations create confusion and pose a major dilemma to the unprepared family and the clinician. This is because there are no medical or ethical guidelines for many of these situations in India. There are two laws related to prenatal diagnosis and termination of pregnancy in India; One is Medical Termination of Pregnancy Act (MTP) of 1971 while the second one is Prenatal Diagnosis and Preimplantation Diagnostic Techniques (PPNDT) act of 1994. MTP act allows termination of pregnancy up to 20 weeks of gestation. When MTP act came into existence, prenatal diagnosis was practically nonexistent. It says that 'the pregnancy can be terminated if there is a substantial risk that if the child were born, it would suffer from such physical or mental abnormalities to be seriously handicapped'. PPNDT act is the recent one. Though the name of the act contains the word 'Prenatal diagnosis'; it is aimed only at prevention of female feticide and is silent about important issues of prenatal diagnosis like indications for prenatal diagnosis and termination of pregnancies with fetuses with birth defects or genetic disorders. There are two important issues related to termination of pregnancy after prenatal detection of birth defect. The first is for what fetal defect termination is justified and the second is the gestational age at which the pregnancy can be terminated. MTP act allows termination of pregnancy below 20 weeks of gestation and many families opt to terminate pregnancies for fetal disorders of varying

severity or uncertain prognosis. After 20 weeks, there is no option of termination of pregnancy. Most of the clinicians and also laypersons may feel that termination of pregnancy at any gestation is justified for lethal disorders like anencephaly, bilateral renal aplasia or lethal skeletal dysplasias. Many fetal malformations and other genetic disorders like arrhythmias, ascites manifest after 20 weeks or may get detected after 20 weeks. Twenty weeks is an arbitrary cut off to give status of an individual to the baby. But the status of the baby in the womb is gradually increasing from an embryo to an individual as the pregnancy advances. Hence, termination of pregnancy for a disorder before 20 weeks may be an easier decision as compared to termination in the later part of the pregnancy for the same disorder. The parents may feel that they have the right to terminate the baby after 20 weeks and they may feel that it is in the interest of the baby by way of avoiding the baby's sufferings. But as the pregnancy advances, the balance tilts from the parents' right to have normal child towards the baby's right as an individual to be born alive. And though the parents may wish to terminate suboptimal babies even after 20 weeks, the indications for terminations in later part of pregnancy have to be taken more seriously. Even though there are some malformations for which late terminations can be considered justified, termination after detection of any or every fetal anomaly can not be allowed after 20 weeks. This discussion shows the limitations of Indian laws for termination of pregnancy after prenatal detection of fetal disorders. Taking into account the advances in the field of prenatal diagnosis over last 2-3 decades, there is a need to modify the existing laws to deal with situations arising due to prenatal diagnosis of treatable birth defects, minor anomalies and prenatal detection of anomalies after 20 weeks, which are not uncommon situations. The need for late terminations has to be realised. But at the same time there have to be proper guidelines to decide the malformations / situations for which termination in the second half of pregnancy can be allowed. Many families opt for terminations after 20 weeks though it is not legally allowed. But these decisions are based on their personal perspectives towards life, birth defects and concepts of right and wrong. Medical fraternity, laypersons, religious and social leaders, legal experts need to debate on these issues to bring up ethical guidelines, based on which new laws can come up and guide the society into this modern world of fetal medicine.

Shubha Phadke
1st October, 2008

Genetic Clinics

Genetic Clinics invites articles related to the field of clinical genetics. Original research articles, approach to common clinical problems, reviews, case reports, letters to the editor, etc are welcome. The articles should be brief and conform to Vancouver style of referencing. We also seek suggestions and constructive criticisms to improve this newsletter. The electronic versions of the articles and correspondences should be mailed to geneticsiap@gmail.com .

This quarterly newsletter is published by the Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow on behalf of Genetics Specialty Chapter of Indian Academy of Pediatrics.

CONGENITAL CATARACT

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Introduction and Prevalence

Cataract is opacification of lens which results in distorted and blurred vision. Cataracts can be defined by the age at onset: a congenital or infantile cataract presents within the first year of life; a juvenile cataract presents within the first decade of life; a presenile cataract presents before the age of about 45 years, and senile or age-related cataract after that. Between 8.3 and 25 percent of congenital cataracts are believed to be inherited. Prevalence of cataract is 1.2 per 10000 neonates. Congenital cataracts are responsible for 15% of childhood blindness and are a leading cause of visual disability in children. Bilateral congenital cataract is genetic in at least 25% of cases. In contrast, unilateral congenital cataract is usually sporadic.[1]

Etiological Classification

Genetically speaking, there are four important categories of cataracts :

A. Isolated hereditary (non syndromic) -70%
B. Associated primarily with ocular disease -15%
C. Associated with multisystem disorder syndromes } -15%
D. Associated with metabolic syndromes

Non-Syndromic Congenital Cataracts

Inherited cataract is known to be clinically and genetically heterogeneous. Eleven cataract morphological phenotypes have been described. Phenotypes are defined by the location and morphology of the lens opacities. Genetic heterogeneity is significant and involvement of more than 30 genes has been identified to date. Some of the implicated genes are represented in table 1. Mutations in the same gene may result in different phenotypes (clinical heterogeneity), and mutations in different genes may be associated with similar phenotypes (genetic heterogeneity). The mode of inheritance is mostly autosomal dominant but autosomal recessive and X-linked modes also occur. Expressivity may be variable and penetrance reduced. In X-linked cataract, carriers may show signs. A precise pedigree analysis and a clinical examination of family members are mandatory for correct genetic counseling[2].

Genes causing isolated congenital cataracts

In 26 of the 39 mapped loci for isolated congenital or infantile cataracts specific genetic defects have been identified. Out of the known genes for cataract, half are crystallins, and about a quarter connexins. The others are genes for heat shock transcription factor-4 (HSF4), aquaporin 0 (AQP0, MIP), and beaded filament structural protein-2 (BFSP2). Additional genes or environmental factors might modify the phenotype of the primary mutation associated with the cataracts.

New disease-causing mutations continue to be identified and now encompass genes encoding a wide variety of different lens proteins. The genes so far identified for hereditary cataracts in both humans and animal models encode structural lens proteins, gap junction proteins, membrane proteins and regulatory proteins involved in lens development. More knowledge of the functional consequences of each mutation are being reported and suggest that lens opacification results not only from precipitation and amyloid-like accumulation of proteins essential for lens transparency but also from interference with their secondary functions. This information will also have implications for the more common age-related cataract, which also has a significant genetic component to its etiology. Genes causing monogenic forms of childhood inherited cataract represent excellent candidate genes for age-related cataract.[4]

Table 1: Human Cataract Loci and Genes on Basis of Morphological Subtypes[2,3]

Morphologic Class	Chromosome	Gene
Volkmann (pulverulent)	1p36	
Coppock	1q21-25	GJA8/connexin 50
Coppock like	2q33-36	gE-crystallin/
	13q11-12	Connexin46
	22q11-12	CRY BB2
Aculeiform	2q33-36	CRY GD
Anterior Polar	14q24-qter, 17p12-13	
Posterior Polar	1pter-p36.1, 16q22.1	
Cerulean	17q24, 22q	CRY BB2
Lamellar	12q14	MIP
Zonular with Y sutural opacities	17q11-22	CRY AB
Total	Xp, 10q	PITX3
Sutural (lamellar) (? Synonymous with NanceHoran syndrome)	Xp22.3-21.13	NHS

Congenital malformations may affect any part of the eye and the ocular adnexas. Developmental defects may occur in isolation or as part of a larger systemic malformation syndrome. Many malformations can severely impair vision, whereas others have only cosmetic significance, and still others cause no symptoms and may go undiscovered or may be noted incidentally on routine eye examination. Table 2 lists the anterior and posterior segment disorders associated with cataract.

Table 2: Cataracts Associated with Primary Ocular Disease

Anterior Segment:

- Aniridia = absent iris (complete or partial)
- Anterior segment mesenchymal dysgenesis
- Granular corneal dystrophy
- Peter's anomaly = central corneal leukoma + cataract - Microcornea = small cornea
- Microphthalmia = small disorganized eye
- Rieger anomaly = iris hypoplasia+ abnormal angle structures

Posterior Segment:

- Choroidemia
- Cone-rod degeneration
- Leber's congenital amaurosis
- Norrie's disease
- Persistent hyperplastic vitreous
- Retinitis Pigmentosa =most common association, cataract develop in 3-4th decade
- Stickler syndrome=hereditary viteroretinopathy (RD + high myopia + cataract)*
- Wagner Syndrome=hyaloideoretinal degeneration+ cataract
- Wagner plus-ectopia lentis + microphthalmia + PHPV* + ASD*+ cong. Glaucoma

Syndromic Congenital Cataracts

Hereditary cataracts may often be associated with systemic disorder or multi-system syndromes:[6]

a) Chromosomal disorders e.g. Down syndrome, Turner syndrome.

b) With skeletal dysplasias e.g. Stickler syndrome, Chondrodysplasia punctata.

c) With central nervous system disorder e.g. Norrie disease, Cockayne syndrome.

d) With renal disease e.g. Lowe syndrome, Alport syndrome.

e) With mandibulo-facial disorder e.g. Nance-Horan cataract-dental syndrome, Oculodento digital syndrome, Hallermann Streiff syndrome.

f) With dermatological disorder e.g. Congenital icthyosis, Incontinentia pigmenti.

g) With metabolic disorder e.g. Galactosemia, Smith -Lemli-Opitz Syndrome.

Children born with the findings of microcephaly, cataracts and microcornea can result not only from a prenatal viral infection, but also from autosomal recessive Mendelian disorders.[7] Micro syndrome (microcephaly, mild microphthalmia, microcornea, congenital cataracts and hypogenitalism in males) should be considered in any infant with congenital cataract.[8,9] The differential diagnosis includes cerebro-oculo-facio-skeletal syndrome (COFS); a syndrome involving cataract, arthrogryposis, microcephaly, and kyphoscoliosis (CAMAK); a syndrome with cataract, microcephaly, failure to thrive, and kyphoscoliosis (CAMFAK); Martsolf syndrome; Neu-Laxova syndrome; Lenz microphthalmia syndrome; and Smith-Lemli-Opitz syndrome.

Cataract with Metabolic Diseases

The cataract associated with metabolic diseases may appear during infancy, but are unlikely to be congenital. In untreated galactosemia, cataract may appear as early as 3 months of age.

Clinical Approach and Management

Accurate diagnosis is the first step in the management of congenital lens abnormalities. In children, cataract is much less common, and is more likely to be associated with some systemic condition. However, no cause is found for the majority of cataracts occurring in children.

Investigations

There is no benefit in doing a large number of tests and investigations on all children with cataract. Table 3 summarizes the clinical approach to a child with cataract. Ask about any illnesses or drugs used during the pregnancy, and find out if the child is developing normally. Remember that all blind children will experience some developmental delay, and this is usually reversed if vision is restored. However, speech and hearing development should be normal. The child should be examined by a pediatrician, who can look for other congenital anomalies, and can determine if the child is fit for general anaesthesia. If the history and examination do not give any clues to the cause of the cataract, there is little point in doing any further investigations.[10,11] Routine investigations include plasma urea and electrolytes, urinary amino acids (to exclude Lowe's syndrome in male infants), urinary reducing sugars (to exclude Galactosemia), and a screen for congenital infection, particularly rubella. Other investigations may be required depending on other clinical findings and will depend on the level of suspicion of a particular disease.

Table 3: Diagnostic approach to a patient with congenital cataract[2]

HISTORY:
Family history of cataracts
Perinatal history for : – Infection e.g. rubella, syphilis, CMV – Drug exposure e.g. corticosteroids, Vit A – Ionizing radiation e.g. X-rays – Prenatal / perinatal metabolic disorder e.g. maternal diabetes – Trauma

Table 3: Contd.

EXAMINATION:
Eye Examination: – Slit lamp evaluation of cataract to know morphology – Retinoscopy – Ophthalmoscopy – Gonioscopy
Examination of parents Evaluation by a Pediatrician/Geneticist for growth, development and associated major and minor malformations
Antibody titers (rubella) / VDRL test
Karyotype (chromosomal anomalies)
Urine: – Urine sugars (Galactosemia, galactokinase deficiency) – Urine microscopy (Alport syndrome) Urine protein (Alport syndrome) – Urine amino acid content (Lowe syndrome) – Urine copper levels (Wilson disease)
Blood: – Blood glucose – Plasma Amino acids (homocystinuria) – Serum: Calcium, phosphorus, alkaline phosphatase (hypoparathyroidism, pseudohypoparathyroidism) – RBC galactokinase activity and GALT Cholesterol pathway enzymes (Smith-Lemli Opitz syndrome, cerebrotendinoxanthomatosis)
X-rays: (Conradi's syndrome)

Treatment

The management of congenital cataract is very different to the treatment of a routine age-related cataract.[12-15] In infants, if the cataract is not removed during the first year of life, the vision will never be fully regained after surgery. In young children, if the aphakia is not corrected, the vision will never develop normally.

When to operate?

The rules for operating on cataract are quite simple. Cataracts should only be removed when:

1. They are interfering with a person's quality of life.
2. There is a reasonable prospect that surgery will lead to a significant improvement in vision.

As a general rule, if a child is behaving and developing normally, do not operate, but keep under review. As the child grows, the visual demands will also increase. For example, a mild cataract may not interfere with playing outside the house when a child is four years old, but does cause problems at school when he or she is learning to read at the age of six or seven. Do not be misled by the red reflex, as children may see remarkably well despite a zonular cataract through which no red reflex is visible. Remember that removing a cataract in a child removes their ability to accommodate. They may be better off with 6/18 and a full range of accommodation than they would be with 6/9 and no depth of field. Although cataract surgery in children should be done as early as possible, if there is real doubt about whether children will benefit, they are unlikely to come to serious harm by waiting a little longer. As they grow older, it becomes easier to test their vision, and to determine if they need an operation.

From the available data, it would appear that the optimal time to remove a dense congenital cataract in an infant and to initiate optical treatment is when the child is 4–6 weeks of age. To remove the cataract before 4 weeks of age appears to increase the risk of the eye developing aphakic glaucoma, whereas waiting beyond 6 weeks of age compromises the visual outcome.[12] There are numerous surgical procedures described for the treatment of cataract including peripheral iridectomy (for central opacities), needling and aspiration, lensectomy, optic captured posterior chamber intraocular lens after phaco-emulsification.[15] Cataract in children is an important cause of childhood blindness and treatment can make a difference if it can be delivered effectively & in time.

Genetic counseling

Genetic counseling in congenital cataract is usually straightforward when the abnormality is confined to the lens and there is a positive family history. Most families show autosomal dominant inheritance and the status of at risk subjects can readily be assigned by careful slit lamp examination after pupillary dilatation. Variability in disease expression is common and asymptomatic subjects should not be assumed to be unaffected. X linked and recessive forms of inherited cataract are rare and may be recognized when there is an appropriate family history. Genetic counseling in isolated cases is more problematic. Most unilateral cataracts are nongenetic but patients with bilateral cataract in whom there is no family history should undergo further investigation to elucidate the cause. Firstly, the parents and the sibs should undergo slit lamp examination to exclude mild congenital opacities; the presence of such opacities will confirm the familial nature of the cataract and allow accurate counseling of recurrence risks. If other family members are normal, the child should be reviewed by a dysmorphologist or pediatrician to rule out any other clinical features that may suggest a multisystem disorder associated with cataract. In the absence of a family history and where investigations prove normal, the risk of recurrence in subsequent pregnancies is extremely small. When counseling adults with congenital cataract about the risk to their offspring, it is again important to review other relatives and where possible examine clinical records to exclude any syndromic forms of cataract or non-genetic aetiology. In adults without a family history, the risk of having an affected child is very small if the cataract is unilateral. The risk is higher in bilateral cases as some may represent new autosomal dominant mutations; the precise risk is difficult to quantify. Many of the adults seeking advice will have had multiple operations in childhood and still have severe visual impairment; they may have reservations about putting their own child through a similar experience. However, improvements in cataract surgery and optical management have resulted in greatly improved visual outcome and multiple operations are rarely necessary. This improved prognosis should be discussed and it is important that the newborn child is examined by an ophthalmologist in the first few weeks of life to exclude cataract as the long-term prognosis in infants that require early surgery is improved if surgery is performed promptly.

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SYNDROMES AND GENES OF CONGENITAL HEART DEFECTS

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Congenital heart disease (CHD) is one of the most common malformations seen in 1% of population.[1] Etiology of CHD may be chromosomal, single gene defect, environmental or interaction of environmental and genetic factors. Currently knowledge of genetics of congenital heart disease is rapidly increasing and is useful in genetic testing and genetic counseling. In this brief overview, some of the common syndromes of congenital heart disease are discussed.

Incidence

Incidence of congenital heart disease ranges from 4-8 per 1000 live births.[1,2] If we include bicuspid aortic valve and tiny/trivial lesions, incidence increases to 19 and 75 per 1000 live births respectively.[3] Incidence even goes higher if prenatally diagnosed, spontaneously aborted fetuses and stillbirths with congenital heart defects are included.

Classification

CHD can be classified into syndromic and non-syndromic (isolated) CHD, based on presence or absence of associated anomalies and / or mental retardation, respectively. Etiologically, CHD can be classified as chromosomal, monogenic / oligogenic and teratogenic. Many cases do not fit into any known syndrome and cause can not be identified.

1) Chromosomal Disorders and Congenital Heart Disease

Incidence of chromosomal abnormalities ranges from 5-12% in live-born with CHD.[2,4] If fetuses with CHD are included, incidence increases to 22-33%, suggestive of loss of fetuses in the form of spontaneous abortions, medical termination and stillbirths.[1,2] Chromosomal disorder should be suspected in any child with congenital heart disease associated with extracardiac malformations, facial dysmorphism with or without mental retardation. Special investigations include fluorescent in situ hybridization (FISH) and array based chromosomal analysis as indicated.

i) Numerical Abnormalities of Autosomes

Trisomy 21 (Down syndrome): Trisomy 21 is one of the common causes of syndromic CHD. Fifty percent of the children with Down syndrome have CHD (Fig 1).[5] In majority, cardiac lesion is atrioventricular canal defect. Parents need to be counseled before surgical correction of CHD that correcting the heart defect does not correct other associated problems, especially mental handicap.

CHD is also seen in more than half of the cases of trisomy 13 and trisomy 18. However, these babies do not usually survive. Many of these cases are prenatally detected due to associated major anomalies.

Fig. 1. A case of Down syndrome

ii) Sex Chromosomal abnormalities

Turner Syndrome: Most often diagnosis of Turner syndrome is made when a female child presents with short stature and delayed puberty. Characteristic clinical features like webbing of neck, increased carrying angle, CHD, increased pigmented nevi, short fourth metacarpal and

renal malformations are seen in only half of the cases. Commonest chromosomal abnormality is 45,X. Incidence of this condition is about 1 in 2500 to 1 in 3000 female live births.

Cardiac malformations are seen in 16-23% of the cases. Common cardiac lesions are coarctation of aorta, bicuspid aortic valve and mitral valve prolapse. Even if initial cardiac evaluation is normal, periodic assessment is necessary to look for aortic root dilatation. Hypertension could be due to either cardiac lesion, renal pathology or unrelated to any underlying organ involvement.

iii) Microdeletion Syndromes

Deletions are the structural chromosomal rearrangements that result from missing a part of the chromosome. Missing part of the chromosome results in hemizygosity or haploinsufficiency of few or many genes. When the deletion is < 4 Mb size, it is not visible by routine G-banded karyotype and then deletion is called a microdeletion. To find such a microdeletion, specialized technique like fluorescence in situ hybridization (FISH) and more recent new technique multiple ligation-dependent probe amplification (MLPA) are used.

DiGeorge syndrome/Velocardiofacial syndrome (DGS/VCFS) (22q11.2 microdeletion)

22q11 microdeletion is one of the most common microdeletion syndromes. DGS, VCFS (Sphrintzen syndrome), Takao syndrome (Conotruncal anomaly face), Strong syndrome are the various names of syndrome reported in the literature and are all due to deletion involving chromosome 22q11.2 region. Incidence of 22q11 deletion ranges from 1 in 4000 to 1 in 6000 live births.[6] Most of the cases are sporadic. Around 5-10% cases are familial, inherited in autosomal dominant fashion. Clinical manifestations in patients with 22q11 deletion are variable, even within the multiple affected members of a family. Major clinical findings in cases with 22q11 deletion include characteristic face, CHD, immune function abnormalities (80%), cleft palate (44%), hypocalcaemia (60%), hypoparathyroidism, and learning difficulties. Characteristic facial features are upslant eyes, puffy eyes, bulbous nasal tip, broad nasal root, hypoplastic alae nasi, small mouth, micrognathia, cup shaped ears and overfolded helix (Fig. 2). Around 75%-80% of the cases have CHD. Tetralogy of Fallot, interrupted aortic arch type B, truncus arteriosus, ventricular septal defect, pulmonary atresia, misaligned ventricular septal defect are the common heart defects seen in 22q11 deletion cases. FISH investigation for 22q11 microdeletion is indicated in cases with characteristic facial features and heart defects. Some centers recommend FISH for 22q11 microdeletion routinely in cases with above mentioned common cardiac defects in view of variable expression, even in the absence of associated facial dysmorphism or other malformations. Irrespective of clinical features in both proband, and parents; FISH for 22q11 microdeletion is tested routinely in both parents of 22q11 microdeletion positive case. If one of the parents is a carrier, extended family screening is necessary either on paternal or maternal side depending upon which parent is positive for 22q11 microdeletion. In cases with one of the parents being positive, then the risk of transmission of the microdeletion to the offspring is 50%.

22q11 deletion cases posted for cardiac surgery should be advised for perioperative calcium monitoring, and irradiated blood transfusion in view of risk of hypocalcaemia and graft-versus-host disease respectively.[7] Other associated features reported are laryngeal web, laryngomalacia, renal anomalies, vertebral segmentation defect, and craniosynostosis. As an adult, around 20-30% of the cases are known to have schizophrenia or schizoaffective disorder.[7]

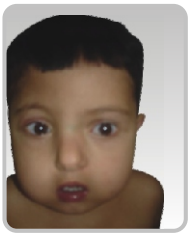

Fig. 2. A case of 22q11 microdeletion with characteristic face

Williams Syndrome

Williams-Beuren syndrome is a microdeletion syndrome, in which chromosome 7q11.23 is deleted. It's a rare disorder with incidence of 1 in 20,000 to 1 in 50,000.[8] Clinically majority are being recognized due to presence of characteristic face (Fig. 3), behavior and congenital heart disease. Characteristic facial features are boggy cheeks, small nose, periorbital fullness, wide mouth, malar hypoplasia, full lips, long philtrum and wide spaced teeth. In infancy, facial features are difficult to make out. Eighty percent of

Williams-Beuren syndrome (WBS) children have cardiovascular anomalies and the most common congenital heart defect is supravalvular aortic stenosis. Seventy-five percent of them have mental retardation; usually mild and almost all have some learning difficulties. Behavior described in children with Williams syndrome is distinct. Often they are described as anxious and overfriendly.[8] Various other clinical manifestations are idiopathic hypercalcemia, feeding difficulties, hypothyroidism, urinary tract malformations, connective tissue abnormality, joint laxity, chronic otitis media, strabismus, hoarse voice and failure to thrive.[8]

FISH with region specific probe (7q11.23) is indicated in cases with characteristic face, heart defects, and behavior. Parental testing is not indicated routinely unlike 22q11 microdeletion cases, unless one of the parents has characteristic clinical features. Most of the cases are sporadic with negligible risk of recurrence. There are reports of familial autosomal dominant inheritance, usually maternal.

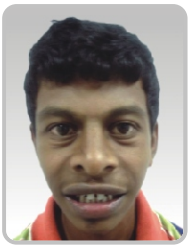

Fig. 3. A case of Williams syndrome with characteristic face

2) Single Gene Disorders and Congenital Heart Disease

Noonan syndrome and related disorders:

Noonan syndrome is one of the commonest causes of syndromic short stature with or without congenital heart disease. Noonan syndrome (NS) is a genetic disorder inherited in an autosomal dominant fashion. Incidence of Noonan syndrome ranges from 1 in 1000 to 1 in 2500 live births as reported in western literature. Clinical manifestations include characteristic face (hypertelorism with down slanting eyes, low set posteriorly rotated ears) (Fig. 4), congenital heart defect, variable degree of mental retardation, undescended testis in males, webbed neck, short stature, chest deformity and bleeding tendencies. Other features include feeding difficulties, café-au-lait spots, pigmented nevi, scoliosis, unexplained hepatosplenomegaly, urinary tract malformations, acute leukemia and myeloproliferative disorders.[9]

Congenital heart disease is seen in 50-80% of the cases. Commonest cardiac lesions are pulmonary stenosis and hypertrophic cardiomyopathy (HCM). Periodic cardiac evaluation is necessary in cases with initial normal cardiac assessment, to find evolving HCM. Majority of the cases are sporadic. The mode of inheritance is autosomal dominant, risk of recurrence in familial cases in siblings and offspring is 50%. In sporadic cases, empiric risk of recurrence in siblings is 1-5%.[10]

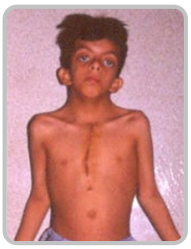

Fig. 4. A case of Noonan syndrome with characteristic face

There are Noonan-like conditions described in the literature with marked overlapping features. Underlying genetic cause explains the overlapping manifestations. Various Noonan-like conditions described are Costello syndrome, cardio-facio-cutaneous syndrome, LEOPARD syndrome, Noonan syndrome with neurofibromatosis and Noonan-like with multiple giant-cell lesion syndrome. These are caused by genes in the RAS-ERK pathway (Table 1); thus explaining phenotypic similarities.

Some common Mendelian (monogenic) syndromes with CHD and their causative genes are given in table 2.

3) Isolated Congenital Heart Disease

With improved molecular technique, single gene origins of CHD are increasingly being identified. Single gene defects are known to cause both syndromic and non-syndromic CHD. Same gene can cause different pattern of cardiac malformation and different genes can cause same heart defect. GJA1 gene mutations are reported in cases with hypoplastic left heart syndrome, atrioventricular canal defects and oculodentodigital syndrome. JAG 1 gene mutations can cause Alagille syndrome and are reported in cases with tetralogy of Fallot. Mutations in NKX2.5, GATA4 are also reported in cases with tetralogy of Fallot,

Table 1: RAS-ERK pathway disorders

SYNDROME	GENE	PROPORTION CAUSED BY THE GENE	HEART DEFECTS	ASSOCIATED FEATURES
Noonan Syndrome	PTPN11 KRAS SOS1 RAF1	50% <5% 10 to 13% 3 to 17%	Pulmonary valve stenosis (PS), Hypertrophic cardiomyopathy (HOCM), ASD	Short stature, down slanting palpebral fissures, webbing of neck, pectus carinatum, pectus excavatum, cryptorchidism
Costello Syndrome	HRAS	80 to 90%	HOCM, Atrial Arrhythmia, PS	Warts/papillomata, Noonan like face
Cardio-facio-cutaneous Syndrome	BRAF MAP2K1 MAP2K2 KRAS	70 to 80% 10 to 15% <5%	HOCM, PS, ASD	Noonan like face, sparse curly hair, large head, coarse facies, short stature, mental retardation
LEOPARD Syndrome	PTPN11 RAF1	80-90% Few	PS, HOCM	Multiple Lentigens, Hypertelorism, Deafness, Conduction defects of heart, Pulmonary Stenosis

Table 2: Monogenic syndromes with CHD

SYNDROME	GENE (Inheritance)	CARDIAC MALFORMATIONS	ASSOCIATED FEATURES
Holt Oram Syndrome	TBX5 (AD)	Atrial Septal Defect	Thumb anomalies, extra carpel bones, radial ray defects
Treacher Collins Syndrome	TCOF1 (AD)	Any CHD	Antimongoloid slant eyes, micortia, coloboma eyelid, hypoplastic zygomatic arch
Asymmetric Crying Face Syndrome	EYA1 (AD)	Ventricular Septal Defect	Congenital hypoplasia of depressor anguli oris, anomalies of head and neck
Johanson Blizzard Syndrome	UBR1 (AR)	Any CHD	Frontal cowlick, spiky hairs
Kabuki make up Syndrome	8p22-8p23 duplication (Sporadic, AD)	Coarctation aorta, Ventricular Septal Defect	Eversion of the lower lateral eyelid, arched eyebrows, lateral 1/3rd sparse/dispersed eyebrows
Thrombocytopenia Absent Radius Syndrome	Locus 1q21.1 (AD)	Conotruncal cardiac defects	Radial aplasia, thrombocytopenia, cow milk intolerance

AD: Autosomal dominant, AR : Autosomal recessive

atrial septal defects and other cardiac malformations. Modifier genes may be one of the factors responsible for the wide spectrum of manifestations due to single underlying defect. Great degree of intrafamilial variability is observed and severe CHD may occur in the sib of a child with minor CHD. At present prediction of exact phenotype based on single gene mutations is difficult. Genotype-phenotype correlation with high accuracy will be more useful in clinical practice. Empiric risks of recurrence in first degree relatives are available.

4) Other Syndromes/Association with CHD

Some combinations of malformations are frequently seen without known cause. This group includes developmental field defects like VACTERAL association, CHARGE association or sporadic syndromes like Goldenhar syndrome, Klippel Fiel syndrome.

In acronym VACTERL individual alphabet stands for, V vertebral anomalies, A-anal atresia, C-cardiac anomalies, TE tracheoesophageal fistula, R renal and radial anomalies. In cases with gastrointestinal anomalies (esophageal atresia/tracheoesophageal fistula) showing two or more VATER anomalies, cardiac defects are seen in 32-65.6% of cases. Most all cases are sporadic but rare cases of familial autosomal dominant transmission have been reported. CHARGE association was initially thought as a association rather than syndrome. Now it has been

found that most affected individuals with CHARGE syndrome have mutations involving the chromodomain helicase DNA-binding protein-7 (CHD7).

Goldenhar syndrome is also known by other names Oculo-auriculo-vertebral syndrome and hemifacial microsomia. Characteristic clinical features are ear tags/microtia, facial asymmetry, epibulbar dermoid, small mandible and vertebral segmentation defect (Fig. 5 and 6). Intelligence is usually normal. CHD are seen in 5-58% of the cases. Most of the cases are sporadic. However familial autosomal dominant inheritance with variable expression is known. Empiric risk of recurrence in sporadic cases is 2-3%.[11]

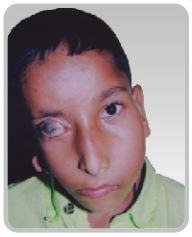

Fig. 5. Goldenhar syndrome with characteristic epibulbar dermoid cyst

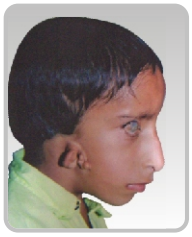

Fig. 6. Ear anomalies in Goldenhar syndrome

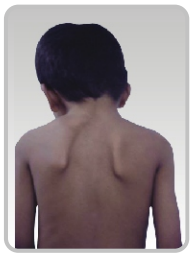

Fig. 7. Klippel-Feil syndrome with high scapula, short neck & low posterior hair line

Klippel-Feil syndrome clinically a heterogeneous disorder. Short neck, limited neck movement and low posterior hair line are the main features (Fig. 7). Common associated manifestations are auricular abnormalities, renal malformations, Sprengel deformity, thenar hypoplasia, webbed neck, thumb abnormalities, polydactyly, additional spinal defects, and congenital heart defects. Usually intelligence is normal. Majority of the cases are sporadic. However families with autosomal recessive and autosomal dominant mode of inheritance have been reported.

5) Teratogenic Agents and Congenital Heart Defects

The agents known to cause CHD are lithium, alcohol, vitamin A, maternal diabetes mellitus, maternal phenylketonuria, maternal infection with rubella and rarely, cytomegalovirus.

GENETIC COUNSELING FOR CONGENITAL HEART DEFECTS

Depending on the etiology/ clinical presentation (syndromic/non-syndromic), the family can be provided anticipatory guidance, available management, referral to special schools for mentally challenged children, accurate risk of recurrence and reproductive options. For chromosomal disorders prenatal diagnosis is possible by karyotyping or FISH. For cases with monogenic syndromes, if a mutation is identified in the affected individual of the family, DNA based prenatal diagnosis can be provided. However, majority of CHD including both syndromic and non-syndromic, the cause remain unidentified. Genetic counseling will be difficult in such cases. Counseling in such situations should also be on giving empiric risk of recurrence, use of periconceptional folic acid. First and second trimester ultrasonography along with fetal echocardiography can detect most of the major cardiac defects. Usefulness and limitations of such scanning should be explained to the parents. Risk to offspring of a parent with isolated non-familial CHD, is around 2-3% in case of paternal CHD and 5-6% if maternal CHD. In CHD of unknown class or etiology, overall risk to siblings is around 2-3% and 10% if there are two affected siblings.

References: (1) Tennstedt C, et al. Heart 1999; 82: 34-9. (2) Ferencz C, et al. Am J Epidemiol 1985; 121: 31-6. (3) Hoffman JI and Kaplan S. J Am Coll Cardiol 2002; 39: 1890-900. (4) Ferencz C, et al. Mount Kisko:Futura 1993; 33-73. (5) Roizen NJ and Patterson D. Lancet 2003; 361: 1281-9. (6) Botto LD, et al. Pediatrics 2003; 112: 101-7. (7) Goldmuntz E. Clin Perinatol 2005; 32: 963-78. (8) Morris CA, et al. J Pediatr 1988; 113: 318-26. (9) Sharland M, et al. Arch Dis Child 1992; 67: 178-83 (10) Sharland M, et al. Am J Med Genet 1993; 45: 437-40. (11) Stoll C, et al. Am J Med Genet 1998; 24: 345-9.

genetic CLINICS

Hutchinson-Gilford Progeria Syndrome

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Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow-226014 (India)

Hutchinson Gilford syndrome is a progeroid condition due to mutation in lamin A gene. Here we present a child with the condition caused by a common mutation.

Case Report

Four and half year old male child born of non-consanguineous marriage presented with loss of hair, eyebrows, joint stiffness in fingers, toes and knees and failure to gain weight. His developmental milestones were otherwise normal. His height was 89 cm (less than 5th centile), head circumference 47 cm and weigh 8.5kg (less than 5th centile). He had the look of an old man with loss of subcutaneous fat. His scalp veins were visible through the skin. He had pointed nose, mandibular hypoplasia, hypodontia, contractures of distal interphalangeal joints, hypoplasia of distal phalanges and nails with pseudoclubbing of fingers and contractures of both knee joints (Fig 1). In addition, he had light colored macules over chest, abdomen and back. Radiographs revealed acral osteolysis. He had generalized osteoporosis, which was confirmed by bone densitometry. He had G608G mutation in lamin A gene that leads to activation of a cryptic splice site in the gene.

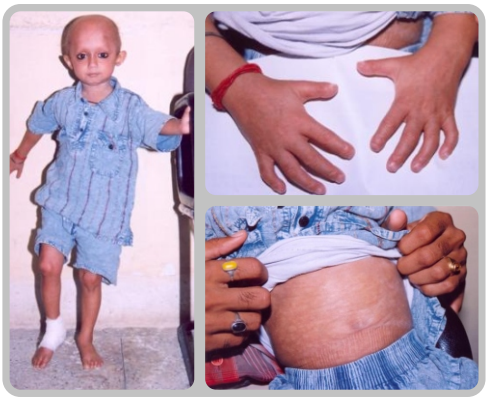


Fig 1. Loss of scalp hair and eyebrows giving old man look. Contractures of fingers and whitish macules over abdomen due to herniation of subcutaneous fat through dermis

Discussion

Hutchinson-Gilford Progeria Syndrome (OMIM 176670) is a progeroid syndrome first described by Jonathan Hutchinson (1886) and Hastings Gilford (1904) in two separate families. The present subject has features of this condition. He also had an unusual skin lesion. The symptoms develop in childhood and resemble accelerated aging. Motor and mental development is usually normal. These patients are prone for early onset severe atherosclerosis and generally succumb between the ages of 6 and 20 due to severe cardiac or cerebro-vascular disease. The condition needs to be differentiated from others with premature aging like Cockayne syndrome, mandibulo acral dysplasia, ectodermal dysplasia, Werner syndrome etc. The G608G mutation seen in this patient is a recurrent de novo point mutation of a single-base substitution with a C>T transition resulting in a silent G-to-G change at codon 608 (608G>G) within exon 11 in lamin A.[1] Though this mutation is due to synonymous mutation, it activates a cryptic splice site and leads to a lamin A that lacks 50 amino acids near the C terminus.

It is also interesting to note that the mutation in the same lamin A gene results in mandibuloacral dysplasia (a progeroid condition), Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy and cardiac conduction defects, lipodystrophy disorders, limb-girdle muscular dystrophy type 1B, Charcot-Marie-Tooth disease type 2B1 and restrictive dermopathy suggesting varied spectrum of phenotype due to mutations in the same gene.[2]

Acknowledgment:
The authors thank Dr Abhimanyu Garg, UT Southwestern Medical Center, Dallas, USA for performing mutation analysis in the present case.

References: (1) Eriksson M, et al. Nature 2003; 423: 293-8. (2) http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=150330, accessed on 17.9.2008.

Contributed by:
Parag M Tamhankar and Ashutosh Gupta

Where to search?[1]

Clinicians and scientists involved in patient care always want to know the places on the internet where they can get the best information about genetic conditions. Uhlman and Guttmacher need to be congratulated for presenting the genetic resources on the internet for clinicians. The article provides addresses of websites giving details of genetics clinics, clinical genetics specialists, disease specific information, patient information and support groups, genetic tests, teratogenesis, guidelines etc. It shows the paths, but exploring them is your responsibility!

Terminating One to Save Another[2]

Twin pregnancies with monochorionic placentation (MC) have a high chance of placental vascular anastomosis between the fetuses and hence interfetal transfusion. The indications of selective feticide in such a pregnancy would be TRAP (twin reversed arterial perfusion sequence), TTTS (twin to twin transfusion syndrome) and discordant IUGR. Feticide is usually done by complete cord occlusion by surgical techniques like ultrasound guided bipolar diathermy or cord ligation. These methods are hampered by various complications like large instrument size, multiple port use, long operating times, and risk of vessel perforation. Interstitial laser therapy is one of the minimally invasive techniques in which the intra-abdominal vessels are targeted instead of cord vessels to minimize the chances of needing a follow-up cord occlusion surgery. Donoghue et al from Imperial College London report a series of MC pregnancies that underwent fetal reduction between 1998 to 2007 by interstitial laser therapy. Thirty pregnancies were included. The fetal loss rates were 27 % per pregnancy. Survival rate in non-reduced fetuses was 68 %. Eight percent of surviving fetuses had aplasia cutis congenita. They concluded that interstitial laser therapy may be a less safe option than radiofrequency ablation another minimally invasive technique.

Mirror mirror on the wall[3]

In the US, people who want to take a closer look at their ownselves are approaching gene-testing firms like deCodeme, 23andme and Navigenics. They are packing off their salivas to these companies in order to know their risks for common diseases like heart disease, breast cancer and hypertension. The modus operandi of these companies is chip-based SNP (single nucleotide polymorphisms) analysis and risk calculations by statistical methods. Some of them also offer information on family lineage and comparison between genomes of two individuals, husband and wife for instance. However this insight into the genetic privacy of individuals is liable to abuse by certain third parties including insurance companies, employment agencies etc. The recent legislation in US named 'Genetic Information Nondiscrimination Act' is a measure to prevent these parties from accessing such information. The ACMG (American College of Medical Genetics) has also tightened the noose by calling for tighter regulation by government agencies to ensure accuracy and reliability of these tests. Another bone of contention is that these tests are self prescribed by individuals and not ordered by clinicians. The companies answered back by appointing their physicians who write these tests on prescription slips. And so the debate goes on….

References: (1) Uhlmann WR and Guttmacher AE. JAMA 2008; 299: 1356-8. (2) O'Donohue K, et al. Prenat Diag 2008; 28: 535-43. (3) Khamsi R. Nat Med 2008; 14: 589.

BIRTH OF genetic CLINICS

It was indeed a great day for all those associated with the activities of the Genetics Specialty chapter of Indian Academy of Pediatrics. The dream of having a newsletter of our chapter became a reality on 27th of July 2008. The occasion was 8th ICMR course on Medical Genetics and Genetic Counseling at Sanjay Gandhi Postgraduate Institute of Medical Sciences at Lucknow. The day was very special for alumni and staff of the department of Medical Genetics who had gathered together at their alma mater. 'Genetic Clinics' was released by Dr. A.K. Mahapatra, the director of the institute. Professor S.S. Agarwal, who almost two decades ago started the first department of medical genetics in India, was the guest of honor. He was very happy to see the department and the specialty grow and outlined the roadmap for medical genetics in India. He wished that the newsletter will create the much needed awareness about the developments in the field to the medical specialists. The function was well attended by the members, well wishers and dignitaries. Genzyme India Private Limited, the sponsor of the newsletter was represented by Mr. Anil Raina.

The first issue of Genetic Clinics is being released by Professor A.K. Mahapatra. Professor Sita Naik, the dean, Professor S.S. Agarwal, editor Dr. Shubha Phadke, head of the department Professor Suraksha Agrawal and Secretary of the chapter Dr. Ratna Dua Puri are also seen.

The participants of 8th ICMR course and the staff of the Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences sport the T-shirt with "Medical Geneticists The 'generation next' Docs" inscribed on it.

gEne Mails

'Genetic Clinics' received an overwhelming response. We thank all of you and seek your constant support and wishes. A few of the comments are published below.

-Editor

I'm so impressed with your newsletter. Congratulations. It is both informative and appropriate for pediatricians. Congratulations. Please keep me on your mailing list!

– Judith G. Hall, OC, MD, FCAHS, Professor Emeritus of Pediatrics and Medical Genetics, BC's Children's Hospital, Vancouver, Canada

I must congratulate you for the excellent newsletter. I would appreciate if it is converted into an international quality journal which is indexed. We really do not have any such journal.

– Dr Anil B Jalan, MD DCH MCPS, NIRMAN, Vashi, Navi Mumbai

I am very happy to see the genetics news letter and it is very informative to the clinicians. Our best wishes and warm regards.

– Jayesh J Sheth, Hon Director, Institute of Human Genetics, FRIGE House, Ahmedabad

Congratulations for this very timely effort. Commendable job and kudos to your team.

– Dr GR Chandak, Senior Scientist and Medical Geneticist, Center for Cellular and Molecular Biology, Hyderabad

Congratulations on your effort. It looks good. Yes, I would appreciate a hard copy too.

– Prochi Madon, PhD, Hon. Geneticist, Genetics Laboratory, Dept. of Assisted Reproduction and Genetics, Jaslok Hospital and Research Centre, Mumbai

Well done Genetics team!! The issue has come out very well. A general pediatrician will not have much knowledge about the genetic tests and when to ask for them. I hope Girish's article will give some insight to all the practising general pediatricians. I am sure all the postgraduate trainee pediatricians will benefit from this. But I don't know how many of them aware of it. I appreciate your commendable job in bringing out this quarterly issue. Wish you all the best.

– Dr Harsha Prasada L, Specialist Registrar in Pediatrics and Neonates, Basildon and Thurrock Hospital NHS trust, Basildon, UK

Congratulations on an wonderful newsletter! The quality of the articles and photos is really commendable! This will surely be a boon to all pediatricians.

– Sheila Mathai, MD,DNB,DM, Professor (Pediatrics) & Neonatologist, Armed Forces Medical College, Pune

Excellent newsletter. The academic content is excellent and the layout is superb, keep it up! It is so nice to see the younger members of IAP doing so well.

– Dr Swati Bhave, Former President of IAP

Dear Shubha Phadke, Congratulations! Such a newsletter is a need of the day. I am quiet impressed with the layout and contents of the newsletter.

– Dr Hema Purandarey, Senior Consultant Geneticist, Mumbai

HEARTY CONGRATULATIONS!! The newsletter looks excellent and I think it is a very good initiative taken by you. I congratulate you all for your efforts. Clinical genetics will get a much needed boost with this.

– Dr Roli Mathur, ICMR, New Delhi

Congratulations on the slick and savvy first issue of Genetic Clinics. I found it extremely useful and worth archiving. Ultrasound practitioners like me will find the polydactyly section serving as a constant ready reference. I look forward to further issues.

– Dr Ashok Khurana, Counsultant in Reproductive Ultrasound, New Delhi

Spare the prick and spoil the child

Newborn screening, mandatory in many western countries, screens up to 20 treatable metabolic disorders from blood sample obtained from a single heel prick.

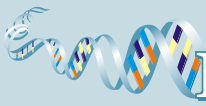
A folate a day keeps the geneticist away

Periconceptional folic acid supplements (0.4 mg once daily) reduces the incidence of fetal neural tube defects by 70 % and is effective in primary prevention

A syndrome in hand is worth two in the bush

Fifty percent of cases presenting with multiple dysmorphic features or malformations do not reach a definitive diagnosis even after extensive investigations.

Contributed by:
Dr Parag Tamhankar



Clinical Manual on Inborn Errors of Metabolism

Members of the National Task Force on Inborn Metabolic Disorders (NTF-IMD) of the Indian Council of Medical Research have brought out a publication titled **"Clinical Manual on Inborn Errors of Metabolism"** edited by Dr Veena Kalra, Dr Madhulika Kabra and Dr Seema Kapoor. The Clinical Manual is priced at Rs 250/- and published by ICMR.

Contact:
The Head, Division of Publication and Information | Indian Council of Medical Research
Ansari Nagar, New Delhi-110029 (India)
Tel. No.: 26588895, 28588980, 26589794 | Fax No.: 26588662
E-mail: icmrhqds@sansad.nic.in | Website: www.icmr.nic.in
The book is very useful for pediatricians and neonatologists.

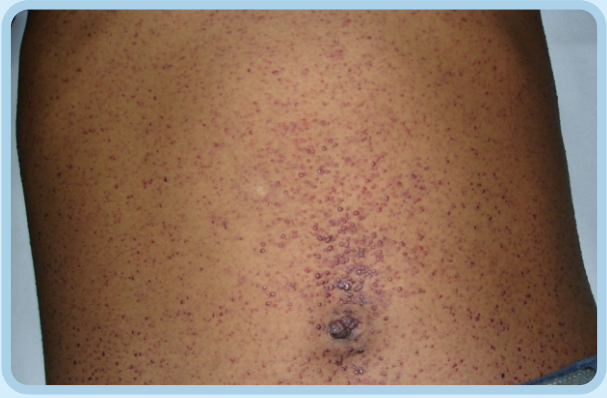
2

Twelve year old male child presented with intermittent pain in great toes of one year duration. He had the skin lesions shown in the photograph.

IDENTIFY THE LESION & THE CONDITION

The response should be sent to geneticsiap@gmail.com

The names of responders with the correct diagnosis will be published in the next issue.



Answer *to the* PhotoQuiz 1 *of the previous issue:*

Goltz syndrome or Focal dermal hypoplasia (OMIM 305600)

The patient had characteristic skin lesions due to herniation of fat through areas of atrophy. In addition the patient has microcephaly, mental retardation, broad nasal tip, hypoplastic ala nasi, ectropion and camptodactyly. The skin lesions initially may be red in color. Other features seen in Goltz syndrome are papillomas, alopecia, oligodontia, microphthalmos, coloboma of iris, cleft lip, cleft palate, syndactyly, polydactyly, dystrophic nails, scoliosis, cardiac anomaly, omphalocele.

Focal dermal hypoplasia is inherited as an X-linked dominant with in utero lethality in males. It is caused by mutations in the gene encoding the human homolog of Drosophila melanogaster Porcupine (PORCN).

Correct response was given by:

Dr Aditi Dagdi, Gainesville, USA

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Membership Application Form

Affix your recent passport size photograph

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5. Telephone: .....
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7. Qualifications
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   Specialty: .....
8. Training in Genetics: .....
9. Area of interest: Dysmorphology / Metabolic disorders / Cytogenetics / Molecular genetics / Prenatal diagnosis / Others .....
10. IAP membership number: .....
11. Demand draft details: (for Rs 1000/= drawn in favor of "Indian Academy of Pediatrics Genetics Specialty Chapter" payable at Lucknow)
    a. Bank: .....
    b. DD number and date: .....
12. Signature with date: .....

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Application No.: ..... Date: ..... Application for membership: ACCEPTED / REJECTED

Membership No.: ..... Receipt No.: .....

Signature of the secretary, genetics specialty chapter of IAP: .....

Send the filled application form to: Dr Shubha R Phadke, Professor, Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow-226014, Uttar Pradesh, India. Email: geneticsiap@gmail.com

Please don't tear. Use a photocopy of this form.

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