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Instructions to authors:

Genetic Clinics is a quarterly newsletter 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. The newsletter aims to provide a forum that enhances the practice and education of medical genetics in India. Articles of interest to the medical professionals in the field of medical genetics are welcome. The broad topics include: Genetic bases of diseases, chromosomal disorders, dysmorphic syndromes, malformations, Mendelian disorders, genetics of complex diseases, genetic testing, prenatal diagnosis, perinatal autopsy, teratogenesis, genetic counseling, laboratory practices, professional issues, psychological aspects, social aspects and legal aspects in the practice of medical genetics. The articles undergo limited peer-review at present and editing of content and style.

The categories of article include:

DeNoVo	Original articles with new findings and development in the field of medical genetics are considered. Word limit is 2000. Restrict the number of references to 15.
GeNeViSTA	Review articles, approach to common genetic problems and opinions from experts in the field are considered. Word limit is 1500-2500. Number of references should not exceed 10.
Clinical Vignettes	Brief case reports not exceeding 1000 words. Limit the number of references to 5.
GeNefOcuS	These are usually invited commentaries on a specific topic by the experts in the field. If you have any idea, please contact the editor.
GeNeXprESS	This is intended to serve as a guide to further reading. Articles of interest to clinicians published recently in leading journals are covered. One paragraph should describe the article.
PhotoQuiz	Good quality photographs of a typical genetic disease or clinical sign. Three to four sentences should describe the condition followed by a question asking the readers to identify the condition. There should be preferably one answer to the query which is unambiguous. The answer should also be provided with one paragraph giving crisp information on the condition.Only the author's name and email id will be published in the journal.
gEne Mails	Letters to the editor discussing the contents of previous issues, comments and suggestions to the editorial board are considered. The section does not ask the response of the author to the comments.
GeneQueries	Clinical case scenarios in practice can be posted and the opinions of experts are sought by the editorial team on further management. The query needs to be precise and unambiguous. Both the question and the answer are published in the same issue.
EvEnTs	Conferences, workshops and continuing medical education programs related to the field of medical genetics are published free of cost. They should be as brief as possible. They are subject to editing of content and style.
GeNeToONs	Cartoons, jokes, humor related to the field of medical genetics are welcome.

Style of references: The articles should conform to Vancouver style of referencing. Only one author is listed. The reference is indicated in the text by the superscripted numbers after the full stop. List only the important references.

Cover page: The cover page should contain the category of article, title, names of the contributors, affiliation and e-mail address for correspondence. Full address for correspondence will not be published and is not necessary.

Generally the articles should include a summary (abstract), introduction, materials/patients and methods results and discussion. The case reports should include a summary, case report and discussion.

Photographs of patients: It is the responsibility of the authors to take written consent from the patient or guardian for publication of photographs.

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Editorial

Rare Genetic Disorders: Not So Rare in India!

Dr Shubha R Phadke

October 2009 witnessed three important conferences for medical geneticists in India. These were the Fourth International Conference on Birth Defects and Disabilities in Developing World (ICBD-2009) held at New Delhi, the second was the 12th Annual Asia Symposium on Lysosomal Storage Disorders (LSDs) held in Taipei, Taiwan and the fourth International Conference on Thalassemia held at New Delhi.

The theme of ICBD 2009 was translating research to cost effective strategies for prevention of birth defects in developing countries. The conference was a collaborative effort of March of Dimes and various other government and non-government agencies It was attended by delegates and experts from various countries across the world. The highlight of the meeting was significant representation by patients and the support groups for various birth defects. The experiences and efforts of the medical and social groups contributing to the betterment of persons with birth defects were overwhelming for the delegates of the conferences. Different aspects of prevention including screening programs, micronutrient supplementation and rehabilitations were discussed. It was a good opportunity for all the concerned to interact, share and plan for the future.

The 12th Asian symposium on LSDs was also well attended by the patients as well as their support groups. It was a part of The International Joint Symposia on Rare Genetic Diseases in Taiwan. Because of availability of enzyme replacement therapy (ERT) for a number of LSDs during the last decade, this annual event has become special and essential. Experts in the field of management of LSDs shared their valuable experiences. The intricacies of individualization of doses, monitoring therapy and supportive therapy were discussed. Availability of ERT calls for early and accurate diagnosis of these disorders by increasing awareness amongst clinicians and may be by neonatal screening. Initial studies on neonatal screening for Pompe disease and Fabry disease were presented. Successful results of treatment by ERT of children of Pompe disease diagnosed early by neonatal screening are very encouraging and show a great promise for LSDs, a group of rare genetic disorders. However, great deal of heterogeneity in the clinical presentation of all LSDs, suggests that it is desirable to know more about the natural course of these diseases before neonatal screening can be implemented.

The Fourth International Conference on Thalassemia was a well planned event with equal participation of patients' families and medical doctors. It was organized by the patient support group – Thalassemics India in collaboration with Sir Gangaram Hospital and Apollo Hospital of New Delhi. The topics covered all aspects of thalassemia management and prevention. The words of experienced specialists from all over the world will definitely make a difference in thalassemia care. The most important part of this conference was the message to the society and the government that a committed patient support group can achieve a lot and the success story of Thalassemics India is a role model for families of other genetic disorders.

It is time that all clinical geneticists and their collaborators from various disciplines sit together and look at the current Indian scenario. There is an urgent need to train the manpower, upgrade the infrastructure for research and patient care and draw public attention to the birth defects. All over the world, neonatal screening is a regular part of preventive medicine for more than 4 decades and now the number of disorders included in neonatal screening has increased to about 40. It is extremely saddening that till today there is no population based program for neonatal screening, prevention for Down syndrome and thalassemia, the latter representing an important health burden in India. The article in this issue by Drs Kabra and Kapoor discusses neonatal screening from an Indian perspective. The recent initiative by Indian Council of Medical Research on neonatal screening, neonatal screening in state of Goa and availability of these tests in some private laboratories are the first few steps taken in this direction.

Understandably, there is no data on prevalence of these disorders in India to assess the gravity of the problem and plan preventive strategies for India. Unless there are well planned population based studies, there can not be data about prevalence, utility and success of screening. Though the prevalence of many of these disorders are in the range 1 in 20000 to 1 in 40000, when absolute numbers are considered, undoubtedly India will have the highest load of these birth defects and genetic disorders. Hence, these (not there) 'rare' genetic disorders are not so 'rare' in India and these genetic disorders should not be neglected by medical fraternity and the government. Patient support groups can play an important role in making their voice reach the policy makers. It is also an opportunity for scientists and agencies from other countries to look for collaborative research work in this field.

Let us hope that the 21st century ushers in a new era for care and research on genetic disorders in India. Wish all the readers an academically satisfying 2010!

ICBD 2009

Shubha Phadke

1st January, 2010

De Sanctis Cacchione Syndrome:
A rare form of Xeroderma Pigmentosum

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SUMMARY

De Sanctis Cacchione syndrome is a rare variant of xeroderma pigmentosum; reported incidence is about 18% to 20% of all cases of xeroderma pigmentosum. A two and half years old boy was brought to medical attention for photosensitive rash, photophobia, and delayed developmental milestones since infancy. Two siblings were affected suggesting autosomal recessive inheritance. He was short for his age and had microcephaly. The child had bilateral telangiectasia in eyes without pigmentary retinopathy and had typical involvement of skin in sun exposed areas. He was hypotonic and deep tendon reflexes were depressed. This case has typical features of De Sanctis Cacchione syndrome.

INTRODUCTION

Xeroderma pigmentosum (XP) is a genetically heterogeneous group of disorders in which photosensitivity, oculocutaneous pigmentation, and neoplasia are manifestations of abnormal DNA repair, with or without progressive neurological impairment.[1] The frequency is one in 250000 population worldwide with higher prevalence in Japan.[2] De Sanctis Cacchione is a rare form of xeroderma pigmentosum with neurological involvement which is seen commonly in complement type XPA and XPD.

CASE REPORT

A two and half years old male child, born of fourth degree consanguineous marriage, was presented in our genetic clinic with delayed development, photosensitivity in the form of skin involvement and photophobia. Photosensitive rash (erythema) followed by peeling leaving behind hyperpigmentation was observed when the boy was exposed to sunlight at the age of one year. There was global developmental delay with developmental quotient of 40% to 50%. Two similarly affected sisters of the proband had expired at the age of three years, suggesting an autosomal recessive inheritance.

The child had microcephaly with head circumference of 41.5 cm (below two standard deviations). His height was 80cms (<5th centile) and weight was 8 Kg (<5th centile). Skin showed peeling with freckles over sun exposed areas. Ocular telangiectasia were present bilaterally (Figure 1). Bilaterally testes were undescended. There was hypotonia in all four limbs and depressed deep tendon reflexes. Rest of the systemic examination was normal. There were no pigmentary changes in retina but cornea showed xerosis. Electroencephalogram was normal.

Clinical diagnosis made was of genodermatosis – Xeroderma Pigmentosum De Sanctis Cacchione syndrome. Parents were counselled about sun protection and importance of follow up for early recognition of premalignant conditions.

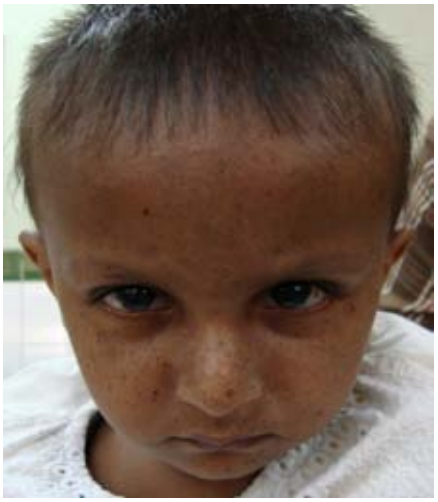

Figure 1a: Face of the child showing pigmentary changes

DISCUSSION

Xeroderma pigmentosum (XP) is a genodermatoses which comprises of inherited skin conditions caused by specific mutations of genes for nucleotide excision repair of damaged DNA. There are seven XP complementation groups of the disorder and one DNA repair gene for each group (XPA to XPG).

De Sanctis Cacchione syndrome (OMIM 278800) is a rare variant of XP where in addition to skin changes of XP, neurological abnormalities are seen.[3] In 1987, Kraemer et al reviewed clinical characteristics of 830 patients with xeroderma pigmentosum.[4] The researchers found neurologic abnormalities in 152 (18%) of these patients. Among patients with nervous system involvement, the most common abnormality was mental retardation (80% of subjects with neurologic involvement), followed by spasticity or ataxia (30% of subjects with neurologic involvement) and microcephaly (24%).[4] Mimaki analyzed 32 Japanese patients with XP-A and neurologic abnormalities and found that mental retardation (21 of 32), microcephaly (17 of 32), and short stature (13 of 32) were the most common neurologic manifestations.[5] This syndrome has also been associated with mutation in the ERCC6 gene; mutations in the same gene have been found to cause Cockayne syndrome type B. In our patient prematurely senile looks of Cockayne syndrome with cataracts, salt and pepper retinopathy was not seen.[1]

XPA complementation group has early neurological abnormality with subtle ocular and skin changes. There is absent or minimal DNA repair capacity of damaged cells. In contrast, XPC has late neurological abnormalities with unscheduled DNA repair capacity between 15% and 30% of normal. Most patients with XPD group present in late childhood or adolescence with neurological and cutaneous problems. Other complementation groups are rare. Neurological abnormalities are due to neuronal loss.

Early diagnosis of this condition is necessary as maximum sun exposure occurs in childhood and thus more skin damage. Without due sun protection, cutaneous malignant changes are seen as early as seven to eight years of age. In a tropical country like India, skin damage may be seen earlier. Maximum skin damage is by UV-B radiations (290 to 320 nm wavelength). Freckles are not a common manifestation of photodamage in Indian population; and if present, it may point to the diagnosis and needs detail evaluation. If sun exposure cannot be entirely avoided, patients should wear long sleeves, use sunscreen with SPF 50, and wear dark glasses. Certain drugs such as oral retinoids, Imiquimode, 5-Fluorouracil, T4 endonucleases in liposomal form can be applied locally to prevent progression of premalignant skin conditions to frank malignancies.[6] Regular follow up at three months intervals is necessary for early recognition of premalignant conditions.

Xeroderma pigmentosum is a progressive condition with a high incidence of cutaneous and systemic malignancies. The average life expectancy is reduced by 30 years. Neoplasms are usually the cause of death.[2] Other complications include progressive neurological involvement and recurrent infections. Our patient had recurrent gastrointestinal infections. Immunological work up was planned but patient succumbed to illness.

Our patient presented with features of De Sanctis Cacchione syndrome. It was interesting to note that the patient had classical neurological involvement and there was a strong family history. This case has been reported for its rarity.

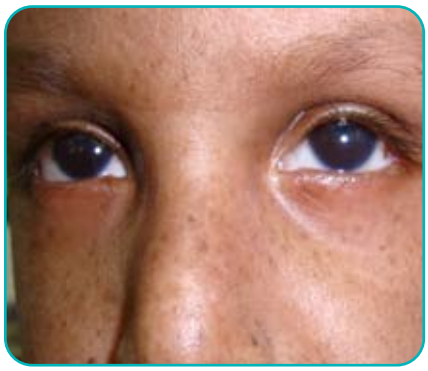

Figure 1b: Skin changes showing freckles. Arrow points to telangiectasia.

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Genetic Evaluation of Male Infertility

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Summary:

Testing for genetic causes of male infertility depends on the clinical and seminal phenotype. A karyotype and analysis for Y-microdeletion are the initial steps in evaluation of non-obstructive azoospermia.

Introduction:

Approximately 15% of couples are infertile and the male factor contributes almost to 30-50% out of which, about 30% of male infertility is idiopathic. Semen analysis is a standard diagnostic test used in the evaluation of male fertility potential till date. With better understanding of the etiology of infertility, it is now clear that the semen findings are poor predictors of male fertility potential. In addition, with the help of modern cytogenetic tools it has been clearly indicated that genetic abnormality can be a cause of male infertility. In most of the occasions, the underlying genetic problem remains unnoticed which can lead to unsuccessful attempts of conceiving through natural means or assisted reproductive technology (ART).

Genetic abnormalities can be chromosomal aberrations, single gene mutations, mitochondrial or multifactorial. Chromosomal aberrations can either be numerical (change in the number of chromosome complements) or structural (deletion, duplication, inversion, translocation etc.) The structural reorganization of the chromosome may be familial or de novo. The effect of structural reorganization on male fertility depends on the morphology and length of the chromosome involved, presence or absence of heterochromatin, frequency of exchanges in the pairing and in the interstitial regions. In the present paper, we discuss the genetic causes of male infertility and the importance of genetic testing in infertile males.

1. Chromosomal abnormalities

A. Numerical abnormalities of sex chromosomes:

The infertile and subfertile men are thought to carry a higher risk of having chromosomal abnormality compared to fertile men. The incidence of sex chromosomal and autosomal disorders in infertile men was observed to be 16 and 5 folds higher respectively than in a fertile male. The most common chromosomal abnormality in infertile men is Klinefelter syndrome (47,XXY) which has a prevalence rate of 1 in 500 in general population. These men have small, firm testes, hyalinization of seminiferous tubules and gynecomastia. They are either azoospermic or have severe oligospermia. A survey suggests that among infertile men, up to 11% of azoospermic and 0.7% of oligospermic men have this chromosomal disorder.[1] Another rare chromosomal disorder is 47,XYY syndrome (incidence 1 in 1000) with a semen profile ranging from azoospermia to normal. Mixed gonadal dysgenesis (45,X / 46,XY) is a condition characterized by development of intersexual gonads and different degrees of gonadal dysgenesis. Most of these individuals are sterile and display features of Turner syndrome.

Studies have now established that there is a direct relation between the semen quality and chromosomal abnormality in infertile men. Van Assche et al have observed that azoospermic men have a higher risk of sex chromosome abnormalities (12.6%), whereas autosome anomalies were most frequent in the oligozoospermic men (3%).[2] Abnormal karyotypes (eg. 47,XYY syndrome) and chromosomal translocations are predominant in approximately 7–13% of patients with idiopathic infertility.[3] Men with 47,XYY karyotype have a normal semen profile. Therefore, idiopathic infertile men are also potential candidates for genetic testing by karyotyping, especially after repeated intrauterine insemination (IUI) or in vitro fertilization (IVF) failures.

B. Autosomal aneuploidies:

It is thought that autosomal disorders as such do not cause infertility. However, it may be associated with poor semen profile as a consequence of other developmental abnormalities. In general monosomies and trisomies of autosomes are not viable which result in abortions. The only surviving trisomies are of chromosome 13, 18 and 21 among which only trisomy 21 survives till puberty. Men with trisomy 21 are either azoospermic or have severe oligospermia. Therefore karyotyping may benefit the men with severe oligospermia who are recruited for ICSI which already has a higher risk of autosomal disorders.

C. Sperm aneuploidy:

Normal males produce a variable proportion of spermatozoa carrying chromosomal abnormalities ranging between 1-15% with more than 90% carrying structural aberrations.[3] Reduced recombination rate and abnormal check point function among the infertile men are thought

to be the major causes for sperm aneuploidy. Fluorescent in situ hybridization (FISH) studies indicate that severely infertile males may have 70% or more spermatozoa that are aneuploid.[4,5] Men with testicular cancer who have undergone radiotherapy and/or chemotherapy treatment may show increased number of aneuploid sperms up to 6 months after the completion of treatment.[6] Aneuploidy screening of spermatozoa may be advised to infertile men with severe morphological defects, non-obstructive azoospermia and in unexplained recurrent pregnancy loss.[7,8,9]

D. Structural aberrations:

The common structural chromosome aberrations detected in infertile men are reciprocal translocation, Robertsonian translocation, deletion, inversion and marker chromosomes. These structural changes can cause derangement in the nucleotide sequence of a gene or group of genes leading to malfunction in gene expression. Males with balanced structural rearrangements of chromosomes may be infertile or may form sperms with imbalanced chromosomal complement leading to recurrent spontaneous abortions in the wife or birth of a child with mental retardation with or without malformations. They can have normal offspring as well, the probability of which will vary in different cases.

Translocation: Infertile men carry 7 times higher incidence of heterozygous autosomal translocation compared to fertile individuals.[10] The incidence of structural and/or functional chromosomal abnormalities is found to be higher in severe oligozoospermia and azoospermia patients than in fertile men. Robertsonian translocation is seen frequently in oligospermic men and rarely in azoospermic men. In majority of the cases the tranlocation is between 13 and 14. The most common recurrent chromosome translocation in infertile men is the Robertsonian translocation between 13 and 14 which is found to be associated with disturbances in spermatogenesis.[11]

SRY gene translocation: SRY (sex determining region Y) gene is located on the short arm of Y chromosome and plays an important role in initiation of male sex determination. Translocation of this gene to short arm of X chromosome results in males with a genotype of 46,XX (incidence 1 in 20,000). These men generally have male gonadal differentiation and may have gynecomastia, ambiguous genitalia, hypospadias. Due to the absence of genes for spermatogenesis in AZF region, spermatogenesis does not occur and hence they are sterile.

Inversion: Infertile men have a high incidence of chromosomal inversion. Paracentric inversions in chromosome 1, 3, 5, 6 and 10 may lead to decreased sperm production through inhibition of meiosis.[10]

2. Y-chromosome microdeletion

The most common type of genetic abnormality in male infertility is Y chromosome microdeletion, which has an incidence of 2-20% in infertile men.[12] The q (long) arm has three different spermatogenesis loci commonly known as azoospermia factors (AZFa, AZFb and AZFc). Microdeletions determine a severe primary testiculopathy resulting in azoospermia or severe oligospermia, and they are more frequent in the AZFc locus. Individuals presenting with severe testiculopathies due to conditions like varicocele or cryptorchidism may also have Yq deletions.[13] Generally, patients with Yq deletion have sperm either in their ejaculate or testes and hence are potential candidates for ART. The genetic defect in such cases is invariably transmitted to the male progeny. All individuals with non-obstructive azoospermia and severe oligospermia should therefore be screened for Yq microdeletions prior to any ART procedure.

3. Single gene disorders and male infertility

Altered sequences of DNA in a single gene or group of genes often result in defective function of the gene/s. These defects may be inherited to the progeny either in dominant or recessive patterns.

Cystic fibrosis: It is an autosomal recessive disorder due to mutation in cystic fibrosis transmembrane regulator (CFTR) gene. More than 95% of adult men with cystic fibrosis are infertile because of obstructive azoospermia and in most if not all, cystic fibrosis is associated with congenital bilateral or unilateral absence of vas deference (CBAVD or CUAVD). Since spermatogenesis is normal in

these individuals, they are potential candidates for ICSI using spermatozoa retrieved from epididymis or testes. In these cases the major risk to offspring is full blown cystic fibrosis if the female partner is heterozygous for a CFTR mutation.[14] Therefore screening of CFTR mutation is strongly recommended in infertile men with CBAVD or CUAVD.

Immotile cilia syndrome: This syndrome is a heterogenous group of autosomal recessive disorders characterized by defect in the ultrastructure of cilia. Infertility due to lack of sperm motility and chronic infections of upper and lower respiratory tract are common in this group of patients.

Hormonal disorders and genetic defects:

Kallmann syndrome: Kallaman syndrome is a very rare disease (1 in 10,000) which can be X-linked recessive or autosomal dominant. The defect in autosomal dominant disease is not known. However, the more common X-linked recessive form is due to the mutation in KAL 1 gene located on the short arm of X chromosome (Xp22.3) which controls the migration of neurons to hypothalamus and olfactory region during embryonic development. Defect in the secretion of gonadotrophin releasing factor from hypothalamus leads to failure in secretion of LH and FSH from anterior pituitary. These patients have hypogonadotrophic hypogonadism with anosmia. Some men may have infertility due to isolated gonadotrophin deficiency which can be treated with hormone supplement therapy. Therefore these men are potential candidates for screening KAL1 gene mutation.

Deficiency of androgen synthesis: These are autosomal recessive inborn errors of androgen synthesis. Deficiency of enzyme 3 beta hydroxysteroid dehydrogenase, 17 alpha hydroxylase (point mutation) or 17 beta hydroxysteroid dehydrogenase results in defective virilization due to impaired testosterone synthesis.

Deficiency of 5 alpha reductase: This enzyme is required for the conversion of testosterone to dihydrotestosterone which is located on short arm of chromosome 2. Mutation in the gene coding for this enzyme results in defective spermatogenesis.

Androgen insensitivity: It is an X-linked recessive disorder due to a defect in the androgen receptor gene located on Xqll-12. The phenotype may range from complete testicular feminization with an immature female phenotype to an apparently normal male with infertility, although the latter is rare. Although it is not mandatory to test androgen receptor gene mutation in men with azoospermia, in cases with severe oligozoospermia and high androgen sensitivity index (ASI), it can be performed as a second step following karyotyping. The ART for men with AR mutation will not affect the male progeny. However, if the female is a carrier of AR mutation, the male offspring are likely to be affected.[13]

Genetic defects in certain pathological situations causing infertility are listed in table 1.

Condition	Mutation
Beta Thalassemia	11p15
Sickle cell anemia	11p15.5
Congenital adrenal hyperplasia	6p21.3
Prader-Willi syndrome	15q11q13
Bardet-Biedl syndrome	11q13, 15q22, 16q21, 3p13, 2q31, 20p12
Kennedy disease	Xq11–12
Juvenile hemachromatosis	1q
FSH hormone/receptor defect	11p13
LH hormone/receptor defect	LH 19q13
Noonan syndrome	12q24.2
Myotonic dystrophy	19q13.2

Table 1. Mutations in pathological conditions associated with male infertility

Genetic counseling:

The purpose of genetic counseling is to educate the couples who wish to have children through assisted reproductive technology about the possible genetic risks to their progeny and the psychological risks to the family. The genetic risk to the offspring is mainly contributed by father's or mother's gametes or sometimes both gametes. Couples with infertility problems are part of a patient population with some of the highest identifiable genetic risks. To enable decision-making, patients need to be informed about the tests available to identify the genetic status of the couple. If an abnormality is identified, professional genetic counseling should be offered with an explanation of the cause of the genetic defect they have been identified and the implications for the health of the progeny.

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Maple Syrup Urine Disease: Importance of Early Diagnosis

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Introduction

Maple syrup urine disease (MSUD, OMIM #248600) also known as branched-chain ketoaciduria, is a disorder affecting the aliphatic or branched chain amino acids. It is caused by a deficiency of branched-chain alpha-ketoacid dehydrogenase complex (BCKD), the second enzyme of the metabolic pathway of the three branched-chain amino acids, leucine, isoleucine, and valine. It is characterized by psychomotor retardation, poor feeding, and a maple syrup odor of the urine. We are presenting our recent patient who was diagnosed reasonably early after birth.

Case report

A female baby was born at term by normal vaginal delivery with normal Apgar scores. Her birth weight was 3.2 kg. She started breast feeding normally after birth. She was born to non-consanguineous Anglo-Celtic parents. She was presented to a regional hospital with lethargy and poor feeding on day 7 of life. She had normal blood ammonia and mild metabolic acidosis. Her blood glucose and lactate were normal. She had negative septic screen. She was transported to our hospital within 2 hours. We got her newborn screening results on the same day. Newborn screen results revealed high xleucine (collective term for isoleucine and leucine) and valine. At presentation, she had florid features of raised cerebral oedema. She was immediately transferred to ICU and ventilated. Her blood and urine samples were sent for further analysis in metabolic laboratory. She had strongly positive test for urine DNPH. She was started on TPN with no protein. She was targeted to have total calories of 120Kcal/kg/d within 4-6 hours of starting of TPN. Keeping in view the diagnosis of MSUD, she was commenced on haemofilteration. Her initial plasma amino acids showed leucine of 2500 micromol/L, isoleucine 400 micromol/L andvaline 1500 micromol/L. These values continued to come down on haemofilteration. She had leucine of 500 micromol/L, isoleucine 300 micromol/L, valine 550 micromol/L after 24 hours of haemofilteration. She was started on nasogastric valine 50 mg/kg/d with aim to increase valine to get ratio of isoleucine: leucine: valine ::1:2:3. She tolerated small feeds of MSUD formula and gradually we increased her MSUD feeds and titrated with TPN. She was extubated after 72 hours of ventilation. At this time she was on full feeds with MSUD formula. She was on sodium supplement to maintain her serum sodium to 140 mmol/L. Expressed breast milk was introduced on day 4 of admission. She continued to have her plasma amino acids checked daily to monitor her levels and to adjust the volume of natural proteins from breast milk. Gradually, EBM was increased to maintain her essential branched chained amino acids to desirable levels (isoleucine 40-100 micromol/L, leucine 200-250 micromol/L, valine 300-400 micromol/L). She was discharged with clear instructions to parents for weekly Guthrie card for amino acids, feeding instructions, and DNPH montoring whenever she has early signs of any intercurrent illness

Discussion

Any newborn that presents with encephalopathy in absence of evidence of birth asphyxia or infections must be investigated for inborn errors of metabolism. In this child, diagnosis was made fairly early with help of newborn screening. First line investigations done in the regional hospital were compatible with the diagnosis of MSUD. However, if newborn screening results were not available at that time, she might have suffered severe brain damage due to delay in diagnosis and treatment.

MSUD occurs in approximately 1 in 185,000 births.[1] It occurs more frequently in inbred populations, such as the Mennonites in Pennsylvania, where the incidence may be as high as 1 in 200 births. The branched-chain amino acids are important precursors to compounds needed for gluconeogenesis, energy production, and synthesis of fatty acids and cholesterol. End-products of their metabolic pathways are acetyl-CoA, acetoacetate, and succinyl-CoA. In the first metabolic step, leucine, isoleucine, and valine are converted into their respective alpha-ketoacids by cytosolic or mitochondrial aminotransferases. Rare cases of branched-chain aminotransferase deficiency have been reported. MSUD is caused by decreased activity of BCKD, the second enzyme in the degradation pathway. This enzyme complex catalyses decarboxylation of the alpha-ketoacids of leucine, isoleucine, and valine to their respective branched-chain acyl-CoAs. The BCKD complex is situated on the inner mitochondrial membrane and consists of three catalytic components (E1, E2, and E3). The

mode of inheritance is autosomal recessive. The genes encoding BCKD complex components E1-alpha, E1-beta, E2, and E3 have been mapped to human chromosomes 19q13.1-q13.2, 6p22-p21, 1p31, and 7q31-q32, respectively, and have been sequenced. The E1 component catalyzes decarboxylation of the three alpha-ketoacids and is mediated by thiamine pyrophosphate (TPP). E1 is comprised of two distinct subunits, E1-alpha and E1-beta, that form an alpha-2-beta-2 heterotetramer. A lipoic acid moiety in the E2 or acyltransferase component helps transfer the branched-chain acyl group from E1 to CoA. The E3 or dehydrogenase component is a flavoprotein. It resets the lipoyl moiety to the active oxidized form. This component is also associated with the alpha-ketoacid dehydrogenase complexes, pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase. Decreased activity of BCKD results in elevation of plasma concentrations of the branched-chain amino acids and corresponding keto acids. A metabolite of isoleucine causes the urine to smell like maple syrup. The neurotoxicity of MSUD is caused primarily by the accumulation of leucine in the plasma and organs, known as leucinosis.[2,3] High leucine concentrations appear to impair regulation of cell volume. This results in decreased serum sodium concentration and increased intracellular water, leading to cerebral edema. Another mechanism of neurotoxicity may be increased production of glutamate, glutamine, and gamma-aminobutyric acid (GABA) caused by the rapid transport of leucine across the blood-brain barrier. [3]

CLINICAL FEATURES — There are five distinct phenotypes of MSUD: classical, intermittent, intermediate, thiamine-responsive, and E3-deficient. In most cases, these do not correlate with specific mutations. However, they can be distinguished based upon age of onset, severity of clinical symptoms, and response to thiamine treatment. Classical MSUD typically presents in newborns. The intermediate, intermittent, and thiamine-responsive forms may present at any time during infancy or childhood, mostly during episodes of stress.[4, 5] Classical MSUD is the most common form of the disorder. Cases have been associated with mutations in the genes for E1-alpha, E1-beta, and E2. Newborns typically develop ketonuria within 48 hours of birth and present with irritability, poor feeding, vomiting, lethargy, and dystonia.[3] By 4-10 days of age, neurologic abnormalities include alternating lethargy and irritability, dystonia, apnea, seizures, and signs of cerebral edema. Episodes of metabolic intoxication may occur in affected older infants or children who usually are controlled by nutritional management.[3] These episodes often are caused by increased catabolism of endogenous protein that may be induced by intercurrent illness, or by exercise, injury, surgery, or fasting. Clinical manifestations include epigastric pain, vomiting, anorexia, and muscle fatigue. Neurologic signs may include hyperactivity, sleep disturbance, stupor, decreased cognitive function, dystonia, and ataxia. Death may occur from cerebral edema and herniation. The most important diagnostic test for MSUD is the measurement of plasma amino acid concentrations. Affected patients have elevated levels of branched-chain amino acids (leucine, isoleucine, and valine). Urine organic acid measurement will detect elevated levels of branched-chain ketoacids, lactate, and pyruvate. Detection using high-pressure liquid chromatography of alloisoleucine, a metabolite of leucine, and 2-oxo-3-methylvaleric acid, is diagnostic for MSUD. However, alloisoleucine may not appear until 6 days of age, even when leucine levels are elevated. Detection of alloisoleucine is also helpful to differentiate MSUD from ketotic hypoglycemia. Branched chain amino acid concentrations may be transiently elevated in ketotic hypoglycemia or in the post-absorptive state, but alloisoleucine will not be present. Classical MSUD in newborn infants is readily detected only by screening using tandem mass spectrometry. However, affected newborns may be symptomatic before the results are available. Newborn screening may not detect milder forms of the disorder.[6] BCKD enzyme activity can be measured in lymphocytes or cultured fibroblasts. However, this test is not necessary for diagnosis. Prenatal diagnosis can be performed by measuring enzyme activity in cultured amniocytes or choriovillus cells. Mutation analysis should be performed in all patients with MSUD, especially when prenatal diagnosis is anticipated for future pregnancies.

MANAGEMENT — Management of MSUD has two components: dietary therapy to promote normal growth and development and prompt treatment of episodes of acute metabolic decompensation.

Dietary therapy — The goal of dietary therapy is to achieve normal plasma concentrations of branched-chain amino acids, especially leucine. This is accomplished by restricting intake of branched-chain amino acids using commercially available formulas and medical food. Sufficient quantities of these amino acids are provided to support normal growth and intellectual development. Dietary restriction is maintained throughout life. Monitoring consists of measurement of plasma amino acid concentrations every one to two weeks for the first 6

to 12 months of age. The intake of leucine can be adjusted for the individual patient according to these measurements. Monitoring can be performed less frequently with increasing age. A target plasma leucine concentration of <300 micromol/L during infancy and the preschool years is recommended to maximize intellectual outcome.[7] In addition to dietary therapy, thiamine (50 to 300 mg/kg) should be given for four weeks to test for thiamine-responsiveness. Supplementation with sodium chloride sometimes may be necessary to help maintain serum sodium concentration in a normal range and avoid cerebral edema. [3]

Metabolic decompensation – Episodes of metabolic decompensation need to be treated aggressively. Plasma and tissue concentrations of leucine should be lowered rapidly by inhibition of protein catabolism and enhancement of protein synthesis. 3 Hyponatremic cerebral edema should be treated with hypertonic saline, mannitol, and furosemide. In rare circumstances, haemofilteration may be needed to remove branched-chain amino acids and keto-acids.[8] Liver transplantation has been reported in a small number of patients with classical MSUD.[9] After transplantation, BCKD activity is similar to mild types of MSUD and patients no longer require dietary restriction. However, the outcome appears to be similar to dietary therapy.

OUTCOME – Normal outcome is possible in MSUD and the best outcomes occur in patients who begin therapy before they become symptomatic or are treated rapidly after symptoms develop. Cognitive outcome appears to be related to plasma leucine concentration. In one retrospective review of patients with classic MSUD, median plasma leucine concentrations during the first six years of life were indirectly correlated with IQ at 6 years of age. [7]

Acute metabolic decompensation can result in brain injury and requires prompt treatment to avoid neurologic sequelae. Even with aggressive treatment, MSUD can be fatal in the newborn period or during decompensations.

Successful pregnancies in patients with MSUD are expected and leucine tolerance increases progressively after 22 weeks gestation.

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GeNeQueRy

Query: We have a couple with recurrent pregnancy Loss. On performing a karyotype analysis of the couple in our laboratory, the female was found to be normal and the male was having 46,XY;15ps+ . Please comment.

-Sathy M Pillai, Mr Arun SR, Remya S. Samad Hospital, via e-mail

Answer: The extra material on the p arm of chromosome 15 is likely to be prominent satellites or double satellites. In that case it is a normal variant and is not likely to be of any clinical consequence. To differentiate whether it is the prominent satellites or some euchromatic material, you need to do Ag NOR staining which specifically stains satellites.

Dr Shubha R Phadke, shubharaophadke@gmail.com

Newborn Screening in India: Are We Ready?

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Population screening of newborns though initiated in the early 1960's is still of increasing interest internationally. The contribution of genetic and congenital conditions to neonatal ill health and survival are being addressed and the 'epidemiologic transition is advancing'. There is a plethora of these rare genetic disorders and it is indeed challenging to decide the disorders to be included in neonatal screening in context of national priority upfront. The practical challenges in implementing and coordinating this screening exercise are many. The neonatal screening program needs to be evaluated from the epidemiological, ethical and financial perspective.

We are going to focus on a few key points that are vital in the implementation of this program. The foremost is that "Is this the right time to start a nationwide neonatal screening program?" At present the Indian economy is progressing and the infectious and nutritional diseases are showing decreasing trends. It was after the World War II with a low GDP that newborn screening (NBS) was initiated in Japan and current literature does not lament that initiative. One can argue that India is a densely populated country with states having varying levels of health care. The Infant Mortality Rate (IMR) which is a vital statistics of the existing health care varies in different states of India from 80 per thousand to as low as 15 per thousand in Kerala. Is it right to withhold the fruits of NBS till this country of multiple sub-states reaches an acceptable IMR? It is well known that the infant mortality due to genetic disorders becomes important as the IMR goes down and after a certain decline, a country must start investing in prevention and treatment of birth defects. It would not be out of place to suggest that it should at least be started in states having an acceptable IMR and later transit to encompass the rest of the nation.

Second key issue of importance is that which disorder/group of disorders should be our primary targets for screening. It is pertinent here to state that this is a challenging issue with no concurrence among scientists across the globe. To be added to this is the lack of true epidemiologic data on the prevalence of these disorders, their natural history and the effectiveness of treatment in the Indian scenario. We have to select disorders which have a high incidence and are easily treatable without considerable economic burden on the family. The screening priority for the entire Asia Pacific Region has been congenital hypothyroidism (CH) and this holds true for India as well. Data suggest its incidence to be as high as 1:1250 (even higher in certain nothern states). Though other patchy data pockets are available; they also reflect a high burden of preventable mental retardation arising as a sequelae of CH. It is prudent here to mention that this has been stressed in Indian literature as early as the 1970's and 80's by pioneers in the field.

CH may be the target for the national front but there are disorders which cause significant mortality and morbidity in defined geo-ethnic areas. Glucose-6-phosphate dehydrogenase deficiency and hematological disorders like sickle cell disease need early intervention in the mapped areas. Congenital adrenal hyperplasia (CAH) has been shown to have a higher incidence in southern states probably due to a higher endogamous marriage rate. So regional targets for screening can be decided based on the available data and the repository could also be used later for analysis of other disorders.

One cannot but mention the WHO framework of Wilson and Jungner which defines criteria for evaluation of the effectiveness of a screening system. Wilson and Jungner in 1968 recommended ten important criteria, which are valid even today, to select a disorder for universal screening. It should be an important health problem, with a well understood natural history, recognizable latent or early symptomatic state, benefit from early treatment, suitable test or examination available for diagnosis, test must be acceptable to the population, intervals of repeating test should be determined, adequate health services for extra workload available, benefits of the test should outweigh risks, and the cost balanced relative to possible expense for medical care. Based on these criteria many countries used role models like PKU and CH but some developed countries are screening for more than 20 disorders. The American College of Medical Genetics has recommended a panel of 29 disorders. Indian Council of Medical Research (ICMR) indeed needs to be applauded for getting couple of brainstorming sessions of experts in the field to narrow their initiative in 5 cities free of cost to CAH and CH. This multicenteric pilot study has been started in Delhi, Chennai, Kolkata, Mumbai and Hyderabad to adjudge prevalence, feasibility and data on high risk screening of sick neonates and infants.

What also needs to be discussed is what technology to use. This has to be decided without pressure from the private firms luring sale of their commercial kits, the

feasibility and ease of testing in smaller labs and cost economics. ELISA or fluoro-immunoassay based tests currently seem to be a cheap and viable option. Tandem Mass Spectrometry which has the potential to simultaneously screen for a host of disorders requires technical expertise, dedicated personnel and identification of the secondary targets of screening apart from political and financial commitment. Currently, region specific labs should take up this to provide diagnosis to sick newborns with suspected metabolic disorders which may direct their management and counseling and build epidemiologic data on the rarer ones.

One cannot end without identifying bottlenecks in implementation of this program. Targeting rural areas where a significant proportion of births occur is indeed a challenge. This would require the involvement of non-government organizations, rural based paramedical workers for field work and translation of effective advocacy material into regional languages with the creation of audiovisual aids to create an informed need for the same. States wtih an existing NBS program sharing their problems and proposing solutions can offer significant help to improve the program.

Second is the availability of political will. We have some news from print media building hopes. In January 2007, the Union territory (UT) of Chandigarh was declared the first UT to fund NBS with a reduced fee for all and free access to the poor. In February 2008, the State of Goa initiated its mandatory NBS using TMS. In February 2009, the union cabinet has reported to have approved a proposal to start a new lab in Kalyani (West Bengal) to launch NBS at large scale. Though patchy it seems that the ministry has given a patient hearing and in all probability what starts moving will ultimately roll. Apart from initiation of the program, we require the commitment of the Government to allow duty free import of foodstuffs and special diets for these patients. Indigenous institutes like Central Food Technology and Research Institute, Mysore should also start manufacturing the special diets to ultimately make it cost viable.

What is also important is the advancement of knowledge regarding these rare disorders by members of our own fraternity. If the primary and secondary care providers become equipped to understand the importance of the screening strategy and the need for confirmatory testing much of the system reform will occur and transit from states to nation will be a smooth one. It is important to integrate genetic training modules in the undergraduate and postgraduate teaching curriculum in order to finally attain what is desirable.

Coverage of nearly 100% of newborns is the ultimate challenge with inherent problems of home deliveries, migrant population, ineffective transit system and uncoordinated tracking mechanism. Pulse polio program has been an eye-opener. If we could integrate existing health infrastructure with financial and political commitment to witness a remarkable decline in Polio, why can't it be foreseen for NBS? We would just like to depart by saying that, "there is a will and there will definitely be a way".

GeNeMails

Thank you for communications. I am happy that you were kind to send such valuable information. I would like to have printed version of them if available.

-Dr BR Nammalwar, via email

The journal is really well brought out and the credit goes to you all.

-Dr Mala Kumar, Lucknow

It (the new issue) sounds good and interesting. Topic on LSD needs more elaboration as there seems to be many more LSDs than thought with vary variable presentation.

-Dr Jayesh J Sheth, Ahmedabad

Congrats for the excellent work. Kindly send me the previous issues.

-Dr Raghav Rao, via email

Fifty years of Down Syndrome and more....

Contributed by:
Dr Parag M Tamhankar

THE FIFTEETH ANNIVERSARY OF THE DISCOVERY OF DOWN SYNDROME[1]

Genetics in Medicine (the official journal of the American College of Medical Genetics) has brought out special articles on Down syndrome on the 50th anniversary of the discovery of the condition. The issue includes a good review on the past, present and the future of research and treatment of Down syndrome, two commentaries and ACMG standards and guidelines on the prenatal screening for Down syndrome that includes first-trimester biochemistry and/or ultrasound measurements. A must read issue for all the medical geneticists!

BOOSTING EGGS MAY HURT SPERMS' EGO[2]

Superovulation or boosting eggs for subfertile women is an indispensable part of assisted reproductive technology (ART). Recent reports have suggested an increased risk of imprinting disorders such as Angelman syndrome and Beckwith Wiedemann syndrome from ART. Oocytes obtained after hormone stimulated cycles may have disturbed mechanisms of epigenetic inheritance. These are thought to lead to alterations in whole-genome/ specific gene methylation patterns primarily of the oocyte genes. Market-Velker et al have further discovered that these disturbances may also alter the methylation patterns in the paternally derived genes. They studied methylation patterns of four genes in in-vivo fertilized blastocyst stage mice embryos derived either after superovulation or spontaneous ovulation. They thus removed two confounding factors namely in-vitro handling and subfertility which may itself disturb imprinting mechanisms. They found disturbances of imprinting in both maternally and paternally derived genes; loss of methylation in Snrpn, Peg3 and Kcnq1ot1, and gain of H19 methylation. The frequency was increased at higher doses of hormones used for oocyte boosting. They thus concluded that superovulation may disturb imprinting acquisition during development of oocytes as well as imprint maintenance during preimplantation.

IS THE RIGHT ONE NOT ALRIGHT?[3]

The prevalence of aortic arch anomalies is approximately 0.1 % of adult population. There are very few studies which correlate prenatal diagnosis of right aortic arch (RAA) with the postnatal outcome. Galindo et al retrospectively analyzed 48 cases of RAA. Group I comprised 18 cases with RAA and vascular ring. Group II comprised 30 cases with mirror image branching (without vascular ring). In group I, 89 % had normal heart; all had normal karyotype and were negative for 22q11 deletion. In group II, 97 % had congenital heart defects, 17 % had chromosomal abnormalities including 22q deletion. Survival at one year of age was significantly higher for group I (89 %) versus group II (57 %). Diagnosis of RAA, associated heart anomalies, underlying chromosomal anomalies is important to assist in counseling of couple.

COPING WITH CONGENITAL DYSERYTHROPOIETIC ANEMIA[4,5]

Congenital dyserythropoietic anemia (CDA) is caused by aberrant cytokinesis in erythroid precursors leading to ineffective erythropoiesis. CDA type II is the most common form of CDA. Individuals with CDA II present with chronic anemia, requiring frequent blood transfusions, splenomegaly and iron overload. Schwarz et al and Bianchi et al independently discovered that the gene SEC23B encoding secretory COPII component is mutated. COPII coated vesicles mediate export of proteins and lipids from the endoplasmic reticulum to the Golgi body. This may account for hypoglycosylation of RBC membrane proteins. Since Codamin--1 the gene accounting for 88 % cases of CDA I is already known, molecular diagnosis, counseling, prenatal diagnosis of CDA will now be possible.

TWO FISTFUL OF GENES FOR CONGENITAL LIMB MALFORMATIONS[6]

Congenital limb malformations (CLM) affect approximately 1 in 500 individuals and are very diverse in etiology, epidemiology and anatomy. Furniss et al screened twelve genes (two fists considering bilateral polydactyly!) (EN1, GLI3, HAND2, HOXD13, ROR2, SALL1, SALL4, ZRS of SHH, SPRY4, TBX5, TWIST1 and WNT7A) for a cohort of 202 cases with CLMs requiring reconstructive surgery. Sequence variations and copy number changes were analyzed. They identified genetic alterations in 23 cases (11%), mutations in GLI3 (5 cases), HOXD13 (5 cases), ZRS of SHH (4 cases), SALL1, SALL4, TBX5 (one case each) and chromosome abnormalities (4 cases), were found. Surprisingly only 5/23 were diagnosed in routine clinical genetics services pointing out that most cases were not referred to clinical genetics services. The authors concluded that CLM cases with more than one limb involved or associated non-limb malformation or positive family history should be referred to clinical genetics services.

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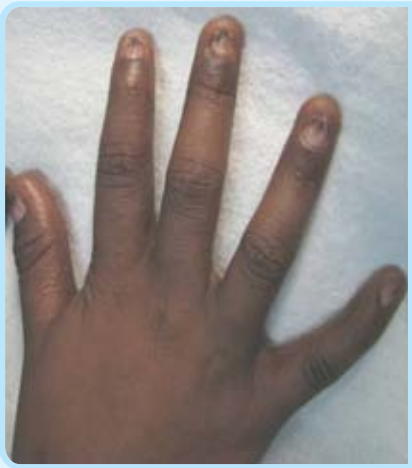
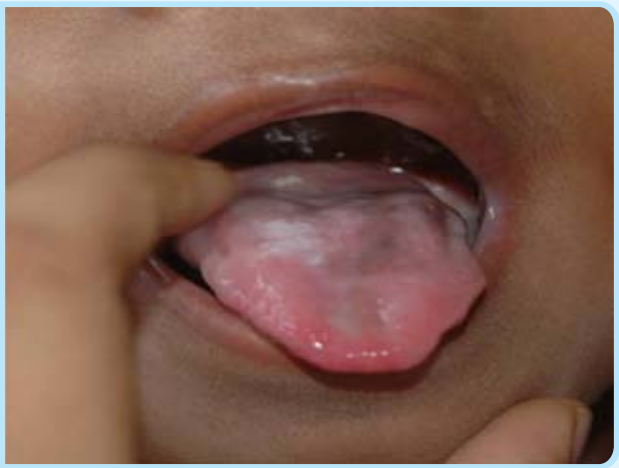
Contributed by: Bansal P, Muranjan M, Kher A, Lahiri KR. Genetic Clinic, Department of Pediatrics, Seth GS Medical College and KEM Hospital, Mumbai.
Email: geneticst@kem.edu

A 7-years old boy presented with severe anemia without hepatosplenomegaly and petechiae. He had required multiple transfusions in the past. He also complained of excessive watering of eyes. Examination of nails and oral cavity clinched the diagnosis. Identify the condition





Answer to the PhotoQuiz 6 of the previous issue:

Morquio Syndrome (OMIM 253000 and 253010)

Morquio syndrome is a lysosomal storage disorder (Mucopolysaccharidosis IV) with predominant spondyloepimetaphyseal dysplasia. There are two types based on the deficient enzyme: Morquio type A due to deficiency of N-acetylgalactosamine-6-sulfate sulfatase (OMIM 253000) and Morquio type B due to deficiency of beta galactosidase (OMIM 253010). Key clinical features include short stature, skeletal dysplasia, dental anomalies and corneal clouding. Intelligence is normal and there is no direct central nervous system involvement, although the skeletal changes may result in neurologic complications. Odontoid hypoplasia leads to atlantoaxial instability. Radiographs reveal severe dysostosis multiplex. The excretion of keratan sulfate is increased in urine. The clinical and radiological features aided by the specific enzyme deficiency confirm the diagnosis of the condition.

Correct responses were given by:

Sunita Bijarnia, Krithika MV

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