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Editorial

Treatments for genetic disorders : From bench to bedside

Identification of genetic defects of monogenic disorders had led to the hope of dramatic and complete cure by gene therapy, but even after at least a couple of decades of research, gene therapy still continues to remain a distant dream. The success of gene therapy for SCID X1 has proved that gene therapy can provide a complete or long term cure for genetic disorders. The long term follow up, of about 11 years, of successfully treated patients with SCID X1 proves this point. However, for many other disorders, a continued, long term expression of a gene in amounts adequate enough to abolish the signs and symptoms has not been possible. But research on genetic disorders has opened up other options of treatment. There has been tremendous increase in the understanding of the pathogenesis of many genetic diseases with identification of the causative genes and their functions. One important breakthrough has been replacement of the defective gene product by recombinant proteins as exemplified by the use of recombinant factor VIII and IX in the treatment of hemophilia. But for other diseases like lysosomal storage disorders, the replacement of deficient protein was not possible for quite some time as the protein could not be targeted to its intracellular site of action. This limitation was overcome with addition of mannose phosphate to the recombinant enzyme which helps the recombinant protein to get internalized into the cells and reach the lysosomes through mannose phosphate receptors on the cell membranes. Development of this strategy helped to bypass the hurdles in the path of successful enzyme replacement therapy and the first successful enzyme replacement therapy (ERT) became available for Gaucher disease about a decade ago. The success was repeated for a few other lysosomal storage disorders and ERT has now become a reality, making a dramatic change in the outcome of these disorders. At present, clinical trials of ERT for several disorders are underway and it is hoped that they would soon become available in clinical practice. These effective therapeutic strategies could be developed as a result of an improved understanding of the various molecular events involved in human physiological and pathological states. The other options for treatment of lysosomal storage disorders include substrate reduction and chaperone therapy to improve folding of the mutated protein and improve its function. The therapies in current practice and other potential treatment modalities likely to become available in the future are discussed in the article on treatment of lysosomal storage disorders in this issue.

Improved understanding of molecular pathology has also opened up other newer strategies for treatment of genetic disorders. These include methods that use or target other molecules involved in the pathway of the genetic disorders. The GENEXPRESS in this issue covers recent research work on some of the new treatment strategies for genetic diseases that are in various stages of clinical trials. The development of new drug options for Marfan syndrome is based on recent research elucidating the pathogenesis of the condition. This also demonstrates how research can be successfully translated into patient care and is an excellent example of translational medicine. Work by Dietz et al has shown that the phenotypic effects of Marfan syndrome such as aortic aneurysms are not primarily due to 'weak connective tissue' as was conventionally believed, but rather due to over activity of the TGF beta pathway, mediated by the abnormal fibrillin gene. Losartan, a commonly used drug, blocks ERK, a protein involved in the TGF beta signaling pathway and thereby inhibits this over activity. Use of this drug has been found to completely eliminate development of aneurysms in mouse models and it is hoped that the dramatic success achieved in mouse models would be replicated in patients with Marfan syndrome as well. As Losartan is a safe drug in humans, a large clinical trial with more than 600 patients has been intiated and the results may take a few years from now.

A similar story is unfolding for a group of disorders known as RASopathies which are caused by genes in the RAS/ MAPK pathway. This group includes Noonan syndrome, Costello syndrome, Cardio-facio-cutaneous syndrome and some other related disorders. There are many features common to them and cardiac involvement is one of them. Treatment of these disorders by drugs manipulating over-activity of the RAS / MAPK pathway is a well thought out strategy. FDA approved drugs inhibiting

molecules in this pathway are already available and planning of drug trials has begun. The article by Rauen et al covered in the GENEXPRESS in this issue has discussed this strategy and various issues involved in planning drug trials for disorders where manifestations begin prenatally and there is a long natural course spread over many decades. Deciding the end point and planning the trial to objectively assess the efficacy of the drug is as challenging as the research in understanding the disease process.

Clinical trials with drugs based on knowledge of the underlying molecular pathology are underway for tuberous sclerosis also and GENEXPRESS has included the article on use of an mTOR inhibitor for treatment of this condition. Drugs based on better understanding of the molecular pathways rather than on replacing a gene or defective protein may be more successful. The twenty-first century is likely to witness dramatic changes in the treatment of genetic disorders which are thought to be incurable at present. Newer treatment strategies are also being explored for diseases like phenylketonuria for which some treatment has been available for decades. Some of these strategies may also be extended to other disorders with a common pathogenesis or mechanism of drug action.

Exciting times are ahead for all patients, doctors and scientists when bench work would reach the bedside providing the most desired and definitive cure for genetic diseases. I wish happy reading to all of you.

Shubha Phadke
1st July, 2011

Echogenic foci in left upper abdominal quadrant in a fetus with Down syndrome

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INTRODUCTION

An area of increased echogenicity in the fetal abdomen is a common ultrasound finding. The grading of echogenicity varies and is significant if the brightness equals that of the bone. Increased echogenicity in fetal abdomen can be seen in the intestines (most common), liver, and kidneys or may be scattered throughout the abdomen as in the case of meconium peritonitis. It is important to make a precise diagnosis which will help in defining the prognosis and take decisions on continuation of the pregnancy. Calcifications in the left upper quadrant are less commonly seen and usually reported to be benign. Here we report a fetus with echogenic foci in the area of spleen whose fluorescence in situ hybridization (FISH) and karyotype showed Down syndrome.

CASE REPORTS

A 30-years-old second gravida was referred to our department. Her ultrasound showed two echogenic foci in the fetus in the area of spleen (Fig 1). She was married non-consanguineously and her first child was normal. There were no other markers of aneuploidy on the ultrasonographic evaluation. There were no associated malformations. There was no polyhydramnios, dilated bowel or features of hydrops. Her previous scan at 18 weeks also showed two echogenic foci in the fetal spleen area. Her first trimester ultrasound had shown nuchal translucency of 1.2 mm and nasal bone of 3.3 mm. Triple test done at 16 weeks suggested low risk of Down syndrome, trisomy 18 and neural tube defect (NTD) (AFP- 0.38 MoM, HCG b- 0.68 MoM, E3- 3.23 MoM). There was no history of bleeding during pregnancy. There was no history of fever or rash during this pregnancy. Her TORCH – IgM serology was negative. There was no history of any drug exposure. Patient was counseled about the association of calcification with aneuploidy, infection or thrombosis or infarcts. Couple opted to go for amniocentesis to exclude chromosomal abnormality.

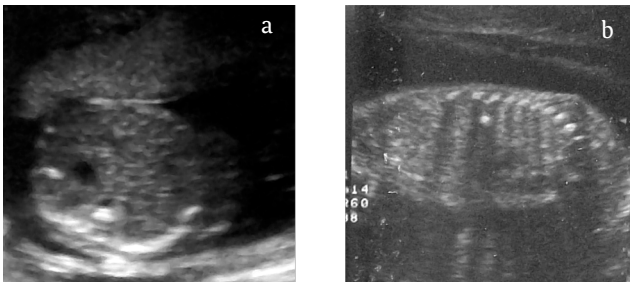

Fig. 1 - Echogenic foci in left quadrant: a) Axial view, b) Sagittal view

Amniocentesis was done to exclude any associated chromosomal abnormality and the FISH analysis showed three signals for chromosome 21(Fig 2). This confirmed Down syndrome in the fetus. Family was counseled about Down syndrome and they chose to abort the pregnancy. Karyotype of fetus showed 46, XY, t(14;21).

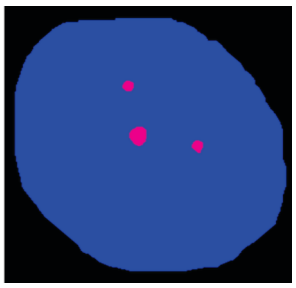

Fig. 2 - Locus specific Indicator probe of chromosome no. 21 showed trisomy 21

DISCUSSION

In this article we report a fetus with echogenic foci in the left upper quadrant of fetal abdomen in the area of spleen. Echogenic foci may be seen in small intestine, liver, kidneys, spleen, heart and adrenals.[1,2,3] Causes include chromosomal abnormalities, infections, cystic fibrosis, vascular accidents such as thrombosis, ischemic infarcts etc. Ji et al have reported 26 fetuses with echogenic foci in left upper quadrant. Of the 26 fetuses, 18

(69%) had a single focus, 7 (27%) had 2 foci, and 1 (4%) had 3 foci.[4] Our fetus had two echogenic foci. Calcification was more commonly seen in liver. Other locations were peritoneal and splenic. Peritoneal calcifications are usually due to meconium peritonitis and there may be features of bowel obstruction on ultrasound such as bowel dilation and polyhydramnios. Our case did not have bowel dilation, polyhydramnios or ascites. Although it is difficult to localize the echogenic focus in-utero, the calcification in our case was in the area of spleen. Ji et al reported that echogenic foci in spleen are uncommon and are usually associated with hepatic lesions. Our case had echogenic focus only in spleen. There was no splenomegaly. The calcification was on the surface of spleen.

We excluded the possibility of infection by IgM TORCH serology, which was negative. Association of echogenic foci with intrauterine infections is reported and they are commonly seen in the liver parenchyma. There may be associated visceromegaly.

Chromosomal abnormality may be associated with echogenic foci in fetal abdomen. Ji et al performed amniocentesis in cases with abnormal biochemical screen and out of 3 cases one had microdeletion [46,XY,del(9)(qh)].[4] Simchen et al reported a case with Down syndrome which had calcification in the liver and left upper quadrant.[5] There was no other feature of aneuploidy on ultrasound. Prognosis for calcification in left upper quadrant has been reported to be favorable in the absence of any associated abnormality.[2,5,6,7,8] Previous reports have stressed the association between additional abnormalities found on ultrasound scanning and chromosome abnormalities. This implies that calcifications found in isolation carry a negligible risk of karyotype abnormalities. In our opinion, the possible association between calcifications in left upper quadrant and chromosome abnormalities should be kept in mind even in isolated cases although the risk is obviously smaller if no other abnormalities are identified.

CONCLUSIONS

Calcifications in left upper quadrant are less commonly described in the fetus. Amniocentesis can be offered to exclude chromosomal abnormalities even in isolated cases.

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Fetal Autopsy in Clinical Practice

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INTRODUCTION

Congenital malformations remain a common cause of perinatal mortality and account for 25-30% of perinatal deaths in developed countries and 10-15% in developing countries like India.[1] Three percent of neonates have a major congenital malformation and 0.7% have multiple congenital malformations.[2] One such mishap creates anxiety in the couple for the fear of similar recurrence in future pregnancies. The recurrence risk of these disorders varies from negligibly low to 25%, depending on the genetic component in the etiology of the disorder. Every effort should be made to identify the etiology of perinatal death so that appropriate genetic counseling can be given. Routine anomaly scan during the antenatal period has become a part of obstetric care and the best time for a fetal malformations scan is at around 18 weeks. Even though an ultrasonogram can give a fairly accurate diagnosis, examination of the terminated fetus for associated anomalies is essential to confirm the diagnosis and look for the cause. This is necessary because some associated malformations can be missed or are undetectable on ultrasound. This can help to reach the correct etiological diagnosis essential for genetic counseling.[3] Fetal loss is a common clinical problem and the families seek and deserve answers regarding the cause of pregnancy loss as the future reproductive decisions of the couples depend on this, which will predict the recurrence risk and may provide options for prevention of a similar mishap.[4]

SITUATIONS WHERE FETAL AUTOPSY IS WARRANTED

Presence of the following problems necessitate the fetal autopsy

1. Presence of external malformations like cleft lip, polydactyly, omphalocoele, cystic hygroma, hydrops fetalis etc.
2. Growth retarded babies are likely to have chromosomal, syndromic or placental causes (recurrence risk varies)
3. Short limbs with narrow thorax: to identify the skeletal dysplasia
4. Macerated fetus
5. Families with previous unexplained fetal loss
6. Fetus terminated because of prenatal ultrasonographic diagnosis of malformations
7. Unexplained fetal loss

APPROACH TO FETAL AUTOPSY

The fetal or neonatal autopsy is a multidisciplinary effort involving the obstetrician, pathologist, radiologist, pediatrician and a clinical geneticist. The causes of fetal loss and perinatal deaths can be genetic and non-genetic (Table 1). The investigations for fetal loss include

Table 1 : Common causes of perinatal death

1.	Chromosomal disorders	Trisomies, triploidy, deletions, duplications
2.	Skeletal dysplasia	Achondrogenesis, short rib polydactyly syndrome, thanatophoric dysplasia, osteogenesis imperfecta type II
3.	Recognizable syndromes	Smith Lemli Opitz syndrome, Meckel Gruber syndrome
4.	Congenital malformations	Renal agenesis, congenital heart disease
5.	Metabolic disorders and single gene disorders	Storage diseases, alpha thalassemia
6.	Non-genetic causes	Placental causes, intrauterine infections, twin gestation, maternal illness

radiograph, chromosomal analysis, fetal autopsy, investigations for infections and genetic metabolic causes, histopathology of the placenta and other fetal tissues as indicated.[5]

Chromosomal analysis should be performed not only in the setting of obvious major malformations but also in fetal hydrops, intrauterine growth retardation, oligohydraminos sequence, macerated fetus and unexplained fetal loss. The sample can be aseptically collected from the cord or fetal heart in a heparinized syringe or a vacutainer. Alternatively a piece of skin can be taken after cleaning with alcohol if tissue culture facilities are available. The sample can be transported at room temperature to a laboratory with a cytogenetic facility within 24 hours. Most of the chromosomally abnormal fetuses are lost in the first trimester. Five percent of stillbirths and neonatal deaths are due to chromosomal abnormalities. A typical presentation is a large cystic hygroma with subcutaneous edema and the commonest chromosomal anomaly associated with this is 45,X (Turner syndrome) (Fig 1). Ten to fifteen percent of

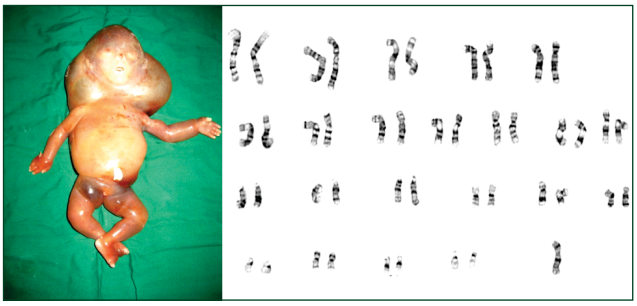

Fig. 1 - A fetus with hydrops fetalis whose karyotype showed 45,X (Turner syndrome)

fetuses with isolated malformations and 30-35% of fetuses with multiple malformations have associated chromosomal anomalies. The malformations more likely to be associated with chromosomal anomalies are omphalocele, holoprosencephaly, duodenal atresia, and congenital heart diseases like atrioventricular septal defect. Anomalies like anencephaly and cleft lip are less likely to be associated with an abnormal karyotype.

Skeletal radiograph is mandatory as a part of the fetal autopsy protocol especially if skeletal dysplasia is suspected due to short limbs.[6] Even though skeletal dysplasia can be suspected by ultrasonogram, accurate diagnosis is possible only with postmortem radiograph often assisted by histopathology. This is important since the recurrence risk varies from negligible to 25%, depending on the type of skeletal dysplasia. Common types of lethal skeletal dysplasias with short limbs are thanatophoric dysplasia, osteogenesis imperfecta and achondrogenesis. The diagnosis can be confirmed by skeletal radiography. Non immune hydrops fetalis can be due to skeletal dysplasia, where the skeletal radiograph will be diagnostic (Fig 2). As genetic defects of many

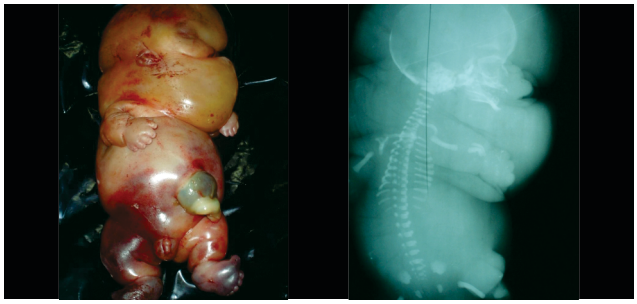

Fig. 2 - A fetus with non-immune hydrops fetalis and short limbs; the skeletal radiograph was suggestive of short rib polydactyly syndrome (SRP)

skeletal dysplasias and malformation syndromes are now known, storing DNA for mutation detection will be useful.

Photographs are essential in documenting the presence or absence of any external malformations. There is also a concept of "limited autopsy" with a photograph and radiograph of the fetus that will help in the diagnosis, if other examination is not possible.[7] Details of autopsy procedures are available in books (Fig 3a and b).[8] Brain

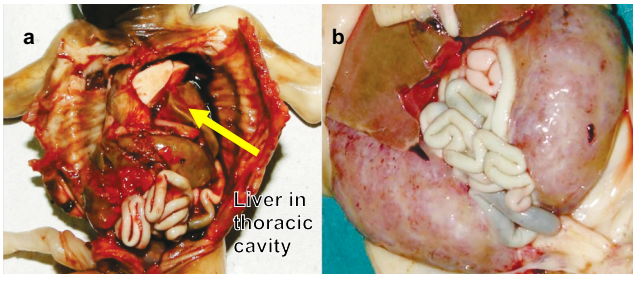

Fig. 3 - Internal malformations (a) Diaphragmatic hernia (b) Polycystic kidneys
Courtesy: Dr. Shubha Phadke

dissection needs good fixation of brain (Fig 4a and b).

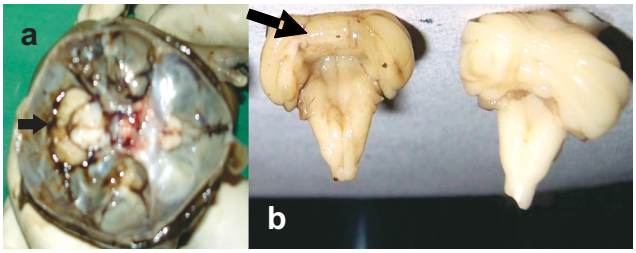

Fig. 4 - Cerebellar malformations (a) 'Banana sign" – Arnold Chiari malformation in a case with meningocele (b) Hypoplasia of inferior cerbellar vermis – normal cerebellar vermis on right side and hypoplastic vermis on left side (indicated by the black arrow)
Courtesy: Dr. Shubha Phadke

Histopathological examination of fetal organs has limited usefulness in fetuses with malformations. An exception to this is the evaluation of fetal renal disease.[8] Renal cystic diseases may be difficult to define on an ultrasound scan since oligohydraminos is usually associated. Moreover the differentiation between infantile (autosomal recessive) polycystic renal disease (recurrence risk of 25%) and cystic renal dysplasia (recurrence risk of 3%) is based on histopathology. Fetal death can be attributed to placental or cord abnormalities in 15% cases. Histopathology, especially of the placenta, is of great importance in cases of intrauterine growth retardation and infection.

UTILITY OF FETAL AUTOPSY

In a good set up with all investigation facilities, an accurate diagnosis is possible in 90% of cases. For cases where definitive diagnosis is reached the exact risk of recurrence can be told to the couple. This may vary from negligible to usually 25% or up to 50% depending on the cause. Neural tube defect can be isolated (recurrence risk is 3%) or may be part of a syndrome like Meckel Gruber syndrome (Fig 5) where the recurrence risk is 25% (Table 2). Negligible risk of recurrence relieves the tension in the family. If prenatal diagnosis is available for the condition, that will help the family.

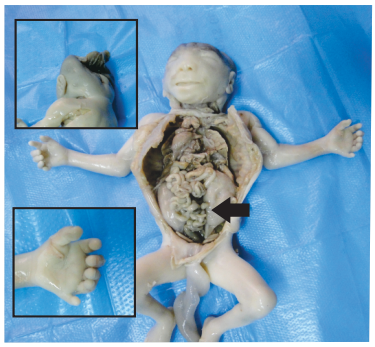

Fig. 5 - A fetus with Meckel Gruber syndrome: Encephalocoele, polydactyly and polycystic kidneys
Courtesy: Dr. Shubha Phadke

Table 2 : Important syndromes associated with Neural tube defects (NTD)

Causes of NTD		Recurrence Risk
Chromosomal anomalies	Trisomy 18 (Edward syndrome)	Negligible
Single gene disorders	Meckel Gruber syndrome	25%
	Jarcho Levine syndrome	25%
	Walker Warburg syndrome	25%
Multifactorial	Isolated Neural tube defect	3-4%

Documentation of malformation helps greatly in genetic counseling and prenatal diagnosis in the next pregnancy. In cases with multiple malformations without any specific diagnosis, same malformations can be looked for in subsequent pregnancies by ultrasound evaluation. In intrauterine deaths and stillbirths without obvious malformations, fetal autopsy helps to rule out many malformation syndromes which may have a high risk of recurrence. The cause of fetal loss in these cases without malformations may be maternal causes leading to chronic placental insufficiency. In such situations, immunological causes, fetal infections, maternal illnesses and factor V Leiden mutation in the mother need to be looked for.

Causes of non-immune hydrops fetalis are numerous including chromosomal anomalies, hematological disorders, metabolic disorders and cardiovascular

disorders.[9] Structural cardiac anomalies, abnormalities of the rhythm and cardiomyopathies have been reported to account for about 25% of cases. The other common causes of hydrops are chromosomal (5 to 33%) and infections (12 to 16%). Congenital malformations, fetal akinesia syndromes and skeletal dysplasias are also reported with fetal hydrops. Genetic hematological conditions like α-thalassemia, pyruvate kinase deficiency and glucose 6 phosphate dehydrogenase deficiency are also reported. Alpha-thalassemia accounts for 28.2% of cases of fetal hydrops in South-East Asia. Many lysosomal storage diseases like Gaucher disease, Morquio syndrome, Sialidosis, Galactosialidosis, etc are known to cause hydrops. In absence of malformations and fetal anemia, the enzyme studies need to be done on fetal lymphocytes or cultured fibroblasts. The combination of examination of the fetus and placenta with the results of microbiological, cytogenetic and metabolic investigations provides an etiological diagnosis for non immune fetal hydrops in 65 to 85 % cases as per various previous studies.

Sporadic malformation syndromes like limb body wall complex and disruption syndromes like amniotic band syndrome have a negligibly low recurrence risk. Thus, the accurate risk of recurrence based on fetal autopsy is very useful for the family.

Examination of fetuses terminated after prenatal diagnosis of malformations is very important. Most of the studies have shown that a post mortem examination confirms the antenatal ultrasound findings in 95-98% of cases.[10] With the present level of accuracy of ultrasonography, a false positive diagnosis is extremely rare, though poor visibility due to oligohydramnios or obesity is an important cause of errors in ultrasonographic diagnosis. However, ultrasonography may miss associated malformations and detection of associated malformations on autopsy may lead to refinement in the etiological diagnosis (Table 3). In a study from India, postmortem examination provided significant additional information in 38% cases, and the change in recurrence risk in 18% cases.[11] In a ten-year retrospective study of autopsy after termination of pregnancy for fetal anomaly, the autopsy confirmed the suspected diagnosis in 72% cases and autopsy added information that lead to refinement of risk of recurrence in 27% cases.[12] Hence, the risk of recurrence based only on the ultrasonographic diagnosis of the fetus may be erroneous in a significant number of cases and autopsy of the fetus after termination of pregnancy is essential for genetic counseling.

Even though autopsy is the best method to detect the cause for perinatal death, there has been a decline in the autopsy rate recently. The various options available for investigations in this situation are reviewed in a recent article.[13] Postmortem magnetic resonance imaging has a useful role in providing structural information of the central nervous system in fetuses and still birth neonates.[14] Another promising approach used in adult postmortem investigation is the use of laparoscopic autopsy which can be tried in perinatal autopsy. However, these options are relatively expensive.

Autopsy facilities are not yet commonly available in India. There is a need to educate obstetricians about the need of fetal autopsy and placental histology for genetic counseling. Our data showed that fetal autopsy results in the Indian scenario are similar to that reported in the literature. Pediatricians with interest in malformation can take up the responsibility of establishment of fetal autopsy facilities in collaboration with a pathologist. Better investigative facilities for chromosomal analysis, metabolic disorders and infections will definitely increase the diagnostic yield, especially in intrauterine death and fetal hydrops. When autopsy is not possible due to ethical and religious reasons, careful examination, a photograph and a radiograph may provide diagnostic information. The uptake of perinatal autopsy services depends on the awareness among obstetricians and pediatricians about its need and utility.

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Management of lysosomal storage disorders: the current status

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INTRODUCTION

Lysosomal storage disorders (LSDs) are a group of inborn errors of metabolism (IEM) characterized by the intra-lysosomal accumulation of complex macro-molecules. Lysosomes are membrane – enclosed compartments within the cytosol of most cell types, which contain acidic hydrolytic enzymes involved in the degradation of certain lipids, proteins, sugars and other substrates. LSDs usually occur due to deficiencies of theses lysosomal enzymes but can also result from defects in key lysosomal membrane proteins, proteins involved in lysosomal enzyme trafficking or lysosomal enzyme activator proteins. The most common causes of morbidity and mortality in LSDs are due to neurological, visceral, cardiovascular and skeletal involvement. At the present time, more than forty different LSDs are known, with a cumulative prevalence of around 1 in 5000 population.[1]

The various modalities tried in the treatment of metabolic disorders in general include substrate restriction (reducing the load on the affected pathway), control of endogenous production of substrate, acceleration of removal of substrate, stimulation of the residual enzyme, enzyme replacement and bone marrow transplantation. Of these different therapeutic modalities, substrate reduction therapy, bone marrow transplantation and enzyme replacement therapy have been found to be more effective options in the management of LSDs. However, as of now, experience pertaining to the use of these treatment options is limited and therefore sufficient data regarding their long – term outcome and efficacy is not available.[2]

The goals of treatment of LSD by either of these methods are reduction in storage of substrate within the cells or organs, favorable alteration in the natural course of the disease and significant reduction in residual disease. More importantly, the burden of treatment should be less than the burden of the disease and the treatment should be safe and affordable.

ENZYME REPLACEMENT THERAPY

Enzyme replacement therapy (ERT) involves exogenous administration of sufficient amounts of the deficient enzyme to effectively clear the accumulated substrate in the patient. Early results were disappointing for ERT as effective targeted delivery of the synthetic enzyme to the lysosomes could not be achieved. But with the discovery of mannose 6-phosphate receptors on the cell surface of macrophages, an effective target for the entry of the exogenous enzyme was found and ERT became a feasible therapeutic option. The recombinant enzymes are modified by post-translational linkage of oligosaccharides containing mannose residues and in some cases, these glycosylated enzymes are additionally phosphorylated at these mannose residues. These enzymes can then bind either to mannose receptors (MR) present on the plasma membrane of mononuclear cells, such as monocytes and macrophages, or to the M6P receptor (M6PR) present on the plasma membrane of many other cell types; following internalization, the enzyme is transported in a vesicle to the pre-lysosomal/endosomal compartment.[3] The first successful ERT developed for Gaucher disease paved the way for ERT for other LSDs. ERT is now available for six LSDs (Gaucher disease, Pompe disease, Fabry disease and mucopolysaccharidoses types I, II and VI) and a number of clinical trials and animal model studies are currently underway for the development of ERT for other LSDs also. The most important drawbacks of ERTs are the cost and their limitation in not being able to reach the central nervous system and few other tissues due to physiological factors such as the blood brain barrier/ absence of the mannose 6-phosphate receptors. Research is ongoing to develop newer strategies of enzyme replacement to overcome these barriers and limitations, such as use of recombinant enzymes designed to target receptors involved in trans-cellular transport of substances across the endothelium in the blood – brain barrier and use of chimeric enzymes targeted to alternative receptors of endocytosis such as transferrin receptor or insulin receptor.[2, 4, 5]

BONE MARROW TRANSPLANTATION

The goal of bone marrow (BMT) or hematopoietic stem cell transplantation (HSCT) is to replace enzyme-deficient macrophages with marrow-derived donor macrophages that can act as an ongoing source of normal enzyme. Though HSCT can modify the disease progression and improve survival in some LSD patients, it is not curative. The chances of a successful engraftment are significantly increased when an HLA matched sibling donor is used as opposed to an unrelated mis-matched donor. The extent of benefit of HSCT also depends on the degree of clinical involvement and the age of the patient at the time of transplantation. HSCT prior to onset of neurological involvement may prevent or delay the neurological manifestations of the LSD, but does not reverse the existing cognitive impairment. The major limitations of HSCT are the cost and the considerable degree of morbidity and mortality due to complications such as graft rejection, inter-current infections and graft – versus –host disease.[6]

SUBSTRATE REDUCTION THERAPY

Substrate reduction therapy (SRT) aims to restore metabolic homeostasis by limiting the amount of substrate precursor synthesized to a level that can be effectively cleared by the mutant enzyme with residual hydrolytic activity, to prevent substrate accumulation. It could be used as the main treatment modality in mild to moderate forms of the disease with less severe enzyme deficiency or it could be given as an adjunct to enzyme replacement therapy in patients with very low residual functional enzyme levels. Some of these substrate reducing drugs are already available clinically such as Miglustat (N-butyl-deoxynojirimycin) which acts by partial inhibition of the glycosphingolipid biosynthetic pathway and is used for the treatment of Gaucher disease.[7] A potential concern regarding the use of SRT is its non-specificity i.e. the substrate whose production is blocked or limited might be important in other metabolic processes also and limiting its synthesis could adversely affect other metabolic pathways.

Amongst the newer approaches being developed for treatment of LSDs is chaperone therapy wherein small molecules, designed to enhance the residual enzyme activity by protecting the mutant enzyme from misfolding and degradation in the cell, are used. This form of therapy is more beneficial for patients with mutations that do not directly affect the enzyme activity or catalytic site but primarily cause enzyme misfolding defects.[8] One such chaperone drug is Amigal (1-deoxygalactonorijimycin) for Fabry disease, for which clinical trials are currently underway.[9] Gene therapy using viral vectors is also being developed as a treatment option, but is either in the conceptual stage or in the animal experimental stage for most LSDs; the underlying principle of gene therapy is somatic gene transfer using viral vectors capable of integrating the exogenous gene sequences into the host genome for prolonged enzyme expression. Another pioneering strategy based on increasing the levels of cytosolic molecules that control intra-cellular trafficking of vesicles, is being developed; this approach would be more effective in the treatment of storage disorders, such as Niemann-Pick disease type C, which are caused by defective lysosomal transporters.[2]

The different levels at which the interventional strategies outlined above act are diagrammatically represented in Figure 1. The specific therapeutic options available for

Fig. 1 - The different levels of intervention for the management of lysosomal storage disorders and the various therapeutic strategies which act at each of these levels.

some of the lysosomal storage disorders are mentioned below.

GAUCHER DISEASE (GD)

The two recombinant glucosylceramidase enzyme preparations currently available commercially for ERT in Gaucher disease are imiglucerase (Cerezyme) produced in Chinese hamster ovary cells and velalglucerase alfa (VPRIV) manufactured in a human cell line. Each formulation is modified to expose the alpha-mannosyl residues for enhanced uptake by the macrophage. Regular intravenous infusions of the recombinant enzyme have been demonstrated to be safe and effective in reversing the features resulting from hematologic and visceral involvement, in reducing bone pain and the frequency of bone crises and in significantly improving the quality of life (Figure 2). However, the currently available ERT does

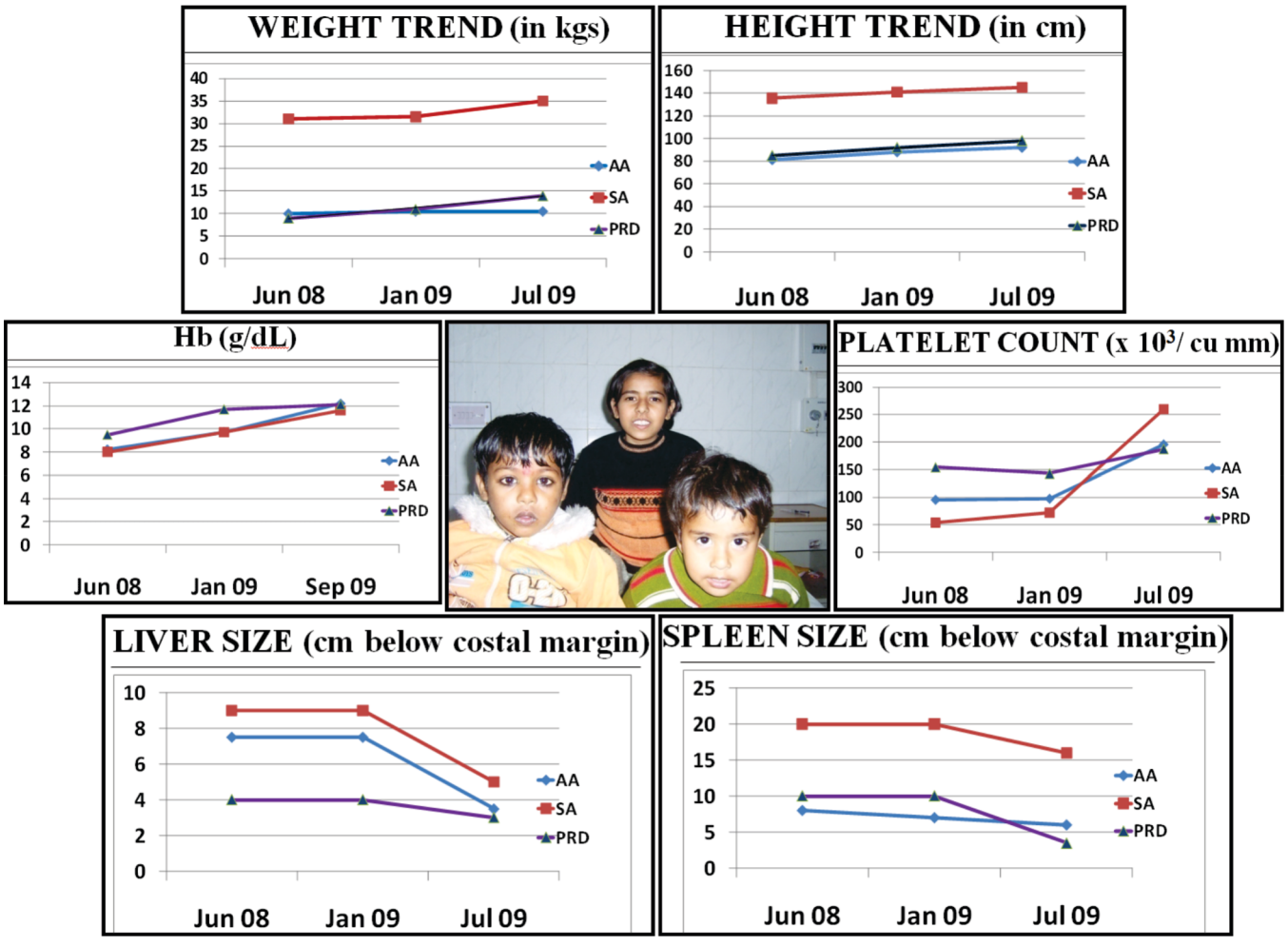

Fig. 2 - Three children with Type I Gaucher disease receiving Enzyme Replacement Therapy. The graphs show the improving trends in weight, height and haematological parameters and reduction in liver and spleen size over a one-year follow up period after initiation of ERT.

not reverse or ameliorate the neurological manifestations of type 2 GD and its benefit in improving the neurological symptoms of type 3 GD is also doubtful.[10]

Miglustat has been found to significantly reduce the liver and spleen volume in mild to moderate forms of GD, but has only a modest benefit in hematological and bone involvement. Bone marrow transplantation is an option for patients with chronic neurologic GD and progressive disease despite ERT. Successful engraftment can correct the metabolic defect, improve blood counts, reduce the increased liver and spleen volume and stabilize neurologic and bone symptoms.[10]

An alternative inhibitor of glucosylceramide synthetase, Eliglustat is currently under clinical evaluation and has been shown in a phase I/II study to be effective in reversing the hematologic, visceral, and skeletal manifestations of GD.11 Clinical trials for a chaperone drug isofagamine for type 1 GD are also currently underway.[12]

NIEMANN – PICK DISEASE (NPD)

Variable results have been reported with BMT in Niemann- Pick disease. While it has been found to reduce the increased liver and spleen volumes, stabilization of the neurologic symptoms following BMT has not been reported. A Phase I enzyme replacement therapy (ERT) trial in adults with NPD B is underway at present. [13]

MUCOPOLYSACCHARIDOSES (MPS)

Bone marrow transplantation or hematopoietic stem cell transplantation (HSCT) has been found to benefit patients with Hurler (MPS IH), Maroteaux-Lamy (MPS VI), and Sly (MPS VII) syndromes. However, unequivocal benefit with HSCT for the neurological and skeletal manifestations of Hunter (MPS II), Sanfilippo (MPS III), and Morquio (MPS IV) syndromes has not been reported. In MPS I, HSCT has been shown to increase the survival, reduce facial coarseness and hepato-splenomegaly, improve hearing and stabilize and improve cardiac function in MPS. However, it does not reduce/ reverse the skeletal manifestations and corneal clouding. The effect of BMT on neuropsychological symptoms is variable and is related to the age and intellectual capacity of the child at the time of the engraftment; in children undergoing BMT before onset of significant developmental delay, it may slow the course of cognitive decline. Children showing significant cognitive impairment prior to undergoing BMT do not appear to benefit developmentally. [14]

ERT is clinically available for MPS types I (Aldurazyme), II (Idursulfase/ Elaprase) and VI (Naglazyme). It has been shown to produce significant improvement in pulmonary function and the six-minute walk test performance, reduce urinary glycosaminoglycan excretion, reduce the liver and spleen volume, and improve growth and joint mobility and decrease sleep apnea. However, it does not have any effect on the neurological features, as it cannot cross the blood – brain barrier. Various approaches to deliver ERT to the CNS are currently being researched; these include CSF instillation of enzyme via direct intra-thecal injection, continuous pumps or microcapsule implants and production of chimeric recombinant proteins designed to cross the blood-brain barrier. [14, 15]

POMPE DISEASE

The ERT available for Pompe disease is Myozyme (alglucosidase alfa). When initiated before the age of six months and before the need for ventilatory assistance, it has been found to improve survival, improve ventilator-independent survival, reduce the cardiac mass and significantly improve the acquisition of motor skills. 16 In some countries, newborn screening for Pompe disease has been started so that treatment can be initiated before the child manifests symptoms. Children put on ERT from the neonatal period onwards have shown very good results with absolutely normal development.

FABRY DISEASE

The two ERTs available for Fabry disease are Fabrazyme (algalsidase beta) and Replagal (algalsidase alpha). ERT has been found to reduce the plasma GL-3 (globotriaosylceramide) concentration by up to 50%, improve the cardiac function, stabilize the renal function, reduce pain in the extremities and improve the quality of life in patients with Fabry disease.[9] A chaperone drug Amigal, has been demonstrated to raise the plasma alpha galactosidase levels in Phase I trials and Phase II trials are now underway.[8]

With availability of ERT there is increasing awareness about the disease amongst clinicians and many more cases of Fabry disease, which is a disease difficult to diagnose clinically, are being picked up. It is important to investigate patients with renal, cardiac and cerebro-vascular disease for Fabry disease at a young age and also to screen asymptomatic relatives of patients with Fabry disease so that treatment can be offered to affected

individuals in the early stages of disease. Though Fabry disease has an X-linked recessive pattern of inheritance, it has been observed that many carrier females may have varying degrees of involvement of organs and may also be candidates for ERT.

METACHROMATIC LEUKODYSTROPHY (MLD)

Bone marrow therapy is presently the only available therapy that has some benefit in treatment of the central nervous system manifestations of MLD, especially in the slowly progressing late-onset forms of MLD i.e. juvenile and adult MLD. The best outcomes are observed in individuals undergoing BMT before the onset of symptoms. BMT has been found to slow central nervous system disease progression but does not alleviate peripheral nervous system manifestations. [17] Effective ERT that can cross the blood-brain barrier has not been developed yet, but recombinant human Arylsulfatase A enzyme is available, and as animal studies have suggested that it may be a useful supplement to other type of therapies, clinical testing of recombinant human enzyme has been started.[18]

GLOBOID CELL LEUKODYSTROPHY (KRABBE DISEASE)

Hematopoietic stem cell transplantation (HSCT) in pre-symptomatic infants and older individuals with mild symptoms helps in improving and preserving cognitive function but does not help in preventing progressive involvement of the peripheral nervous system. The identification of newborns with Krabbe disease by newborn screening would help in early HSCT before onset of neurologic damage.[17] ERT for Krabbe disease is being tried in animal models.

Newer advances in nanotechnology are now being made use of in development of strategies for organ targeting, controlled circulation, effective intra-cellular trafficking and release of lysosomal enzymes. [2] With all these newly emerging approaches, it is hoped that comprehensive treatment modalities would become available for all the lysosomal storage disorders in the not so distant future.

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Familial Infertility : A Case Report

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INTRODUCTION

Y chromosome microdeletions are an important cause of male infertility. In this era of Assisted Reproductive Techniques (ART), identification of Y chromosome microdeletions is important as these individuals can father children with the help of Intra Cytoplasmic Sperm Injection (ICSI).[1] But in this situation the microdeletions and hence the infertility will be transmitted to the male offspring. We report a family with four infertile brothers with confirmed Y-chromosome microdeletions. Familial Y-chromosome microdeletions, though reported, are extremely rare without ICSI.[2,3] The causes of familial transmission of Y microdeletions and the genetic counseling to be provided prior to ART are discussed in this report.

CASE REPORT

A 39-year-old male, was referred to the medical genetics service by the treating obstetrician for the evaluation of severe oligospermia and associated infertility. He was born of a non-consanguineous marriage and was second in birth order. He had 3 brothers and a sister. All the male sibs had similar complaints of infertility due to severe oligospermia. One of the siblings had opted for ICSI; another had an adopted child while the third sib was issueless. The female sib had normal fertility with two offspring. He had unremarkable physical examination with normal secondary sexual characteristics.

Investigations showed normal hemogram and routine blood chemistry analysis. Serum testosterone level was normal with normal serum levels of luteinizing hormone, thyroxin, thyroid stimulating hormone and prolactin levels but the follicle stimulating hormone level was high – 18.57 (normal – 1.24- 7.8 U/L). Semen analysis showed normal volume, viscosity and reaction. Sperm liquefaction time was 10 minutes and aggregation was absent. Sperm count was 0.01 million/ml and motility was only 2% (1% active and 1% showing sluggish motility). Karyotype at 550 band level was 46, XY suggesting a normal male karyotype.

PCR METHODOLOGY

A multiplex PCR with sequence tagged sites (STS) for 6 Azoospermia Factor (AZF) loci spanning the AZFa, AZFb and AZFc regions was used. Fertile male and female samples were used as positive and negative controls. Primer set has been designed by Simoni et al.[4] The various STS used for the AZF regions were:

AZFa : sY84, sY86

AZFb : sY127, sY134

AZFc : sY254, sY255

Multiplex PCR for Y chromosome microdeletions in the proband defined deletions in STS 153, 254 and 255 i.e. the AZFc region.

DISCUSSION

Infertility affects 15-20% of the couples of which 50% could be attributed to factors present in the male partner. A cause is usually defined in approximately half of them which could be due to genetic as well as other less well defined multifactorial causes.

Approximately 5%-10% of men with unexplained infertility associated with azoospermia/oligozoospermia and/or abnormalities of sperm morphology/motility, have chromosomal abnormalities, mostly involving the sex chromosomes. Balanced rearrangements of autosomes are also known to be associated with oligospermia. Other common genetic cause of infertility is microdeletions on Y chromosome regions known as Azoospermia Factor (AZF) regions. Molecular testing reveals microdeletions of the long arm of the Y chromosome in another 5%-10% of these men. Ferlin et al, on reviewing 3,073 infertile men defined the prevalence of microdeletions of Y chromosome at 3.2% in unselected infertile cases, 8.3% with non- obstructive azoospermia and 5.5% in men with severe oligospermia.[5]

The diagnosis of Y infertility is suspected in otherwise healthy males with azoospermia or oligozoospermia and/or abnormal sperm morphology/motility for whom

other causes of infertility have been eliminated. It could be due to either deletions in the Azoospermia factors a, b and c regions or single gene mutation in the USP9Y gene.

Originally, three AZF regions i.e AZFa, AZFb, AZFc were identified on the long arm of the Y chromosome. But with further studies, AZFa and AZFb were found to be overlapping (Fig.2). A more appropriate nomenclature for the type of deletion has thus been adopted which takes into consideration the names of the flanking repeats.[6,7]

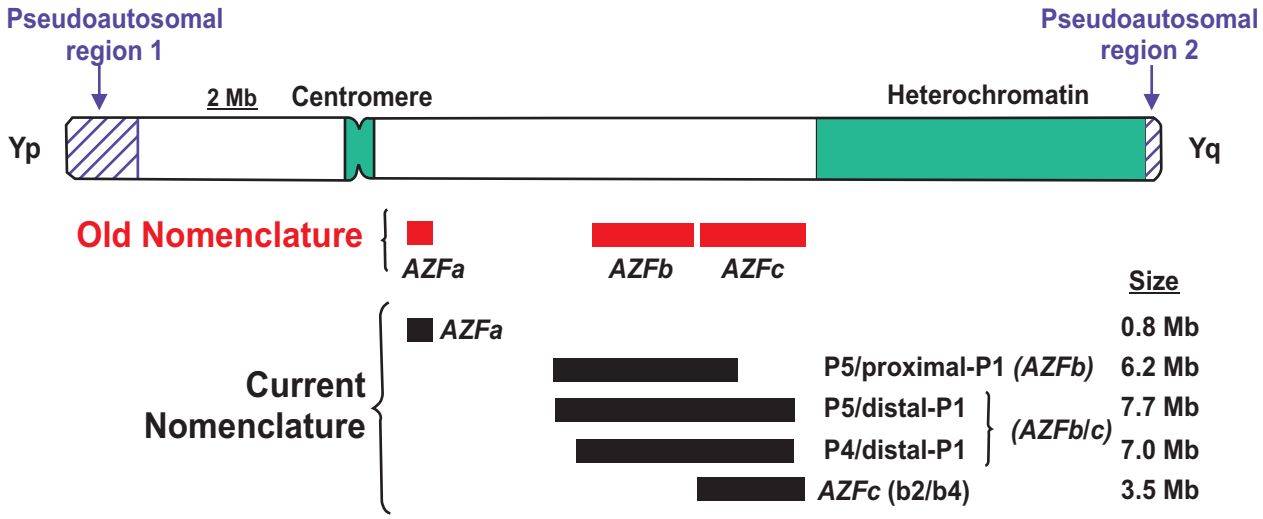

Fig. 1 - Figure showing locations of AZF regions on long arm of Y chromosome with previously defined regions AZFa, AZFb, and AZFc and the position of recurrent deletions currently defined on the basis of the flanking palindromic repeats.

IMPLICATIONS FOR THE PROBAND AND FAMILY

The deletions reported in this patient together with the similar history of infertility and severe oligospermia in all the male sibs points towards a familial cause of infertility. The microdeletion on Y chromosome was detected in the proband and since similar phenotype is present in the brothers, they too most likely harbour the same microdeletions of the Y chromosome. Most of the cases of these deletions are sporadic as these individuals are infertile and hence not transmitted to the next generation. Rarely within a family, the same Y chromosome deletions can cause infertility in some individuals but not in others.[7,8] Hence , some fertile men with deletions of the AZF regions have fathered sons who are infertile which could be attributed to variable penetrance and age dependent decline in fertility. Also, a father could be mosaic for the of the AZF regions; however, this situation has not yet been reported.

The brothers and father in this case need to be screened for the deletions as well. While putting forth the option of assisted techniques of reproduction (ICSI in this case), the associated high risk of transmitting the deletion to the male offspring and resulting infertility should be explained. Female fetuses on the other hand will have normal fertility with no increased risk of congenital abnormalities. Since deletions can be expressed differently in family members, male relatives (e.g., paternal uncles and their sons) may be at risk and thus can be offered genetic counseling and genetic testing too.

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One step forward: from diagnostics to therapeutics

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COSTELLO AND CARDIO-FACIO-CUTANEOUS SYNDROMES: MOVING TOWARDS CLINICAL TRIALS IN RASOPATHIES[1]

RASopathies, a term given to a large group of disorders, include Noonan syndrome (NS), LEOPARD syndrome, capillary malformation-AV malformation syndrome, neurofibromatosis type 1 (NF1), Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFC), and Legius syndrome. These syndromes are caused by germline mutation in various genes encoding components of the Ras/MAPK pathway. All these disorders have overlapping features of various systems with an increased risk of cancer. With understanding of the Ras/MAPK pathway, this group of syndromes has become an ideal multiple congenital anomaly model system for studying the effects of modifying signal transduction in genetic disorders. Emerging data from mouse models with an activated Ras pathway have supported the notion that phenotypes can be successfully normalized in both the prenatal and postnatal period by manipulating Ras/MAPK activity. There are many small molecule therapeutic drugs that are in development or undergoing clinical trials, of which some are already FDA-approved. One such drug is sorafenib which is an inhibitor of RAF (a molecule of the Ras/MAPK pathway), which has been approved for treatment of hepatocellular and renal cell cancer.

EVEROLIMUS FOR SUBEPENDYMAL GIANT CELL ASTROCYTOMAS IN TUBEROUS SCLEROSIS COMPLEX[2]

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by multiple hamartomas in various organs, including the brain. TSC is associated with severe and refractory epilepsy, mental retardation, psychiatric disease, and subependymal giant-cell astrocytomas (SGAs). TSC is caused by dysregulation of the mammalian target of rapamycin (mTOR), a protein responsible for important cellular processes including growth, proliferation, and protein translation. Everolimus, an mTOR inhibitor, has a new role in the treatment of SGA in TSC, with patients receiving Everolimus, experiencing a meaningful reduction in tumor volume, decreased hydrocephalus and intracranial pressure, and a decrease in seizure frequency. This is an example of the clinical application of molecular medicine, whereby, the understanding of molecular mechanism of a disease has been utilized for tailored therapeutics.

PHENYLKETONURIA AS A MODEL FOR PROTEIN MISFOLDING DISEASES AND FOR THE DEVELOPMENT OF NEXT GENERATION ORPHAN DRUGS FOR PATIENTS WITH INBORN ERRORS OF METABOLISM[3]

Phenylketonuria is caused by a deficiency of hepatic phenylalanine-4-hydroxylase due to mutations in the phenylalanine hydroxylase (PAH) gene. In the early 1950s, Dr Horst Bickel successfully developed a low-phenylalanine diet for patients suffering from what was considered an untreatable disorder. These concepts were transferred to other inborn errors of metabolism and led to a significant reduction in morbidity and to an improvement in the quality of life of affected individuals. Now again, recognition of tetrahydrobiopterin as an option to treat these individuals pharmacologically and approval of this drug, have opened the doors for a systematic development of a new class of pharmaceutical products. These pharmacological chaperones are likely to correct misfolding of proteins involved in numerous genetic and non-genetic diseases. Various missense mutations in the phenylalanine hydroxylase gene cause misfolding of protein which lead to disturbed oligomerization, decreased stability, and accelerated degradation of variant PAH proteins. In vitro studies on recombinantly expressed PAH pointed to stabilization of

the misfolded protein by BH4 against denaturation and degradation. This leads to rescue of the biochemical phenotype and enzyme function in vivo. A number of inborn errors of metabolism including various lysosomal storage disorders, fatty acid oxidation defects etc. have now been recognized to be associated with protein misfolding and loss of function. They can therefore be considered excellent candidates for pharmacological chaperone therapy.

FRIGHTENING RISK OF MARFAN SYNDROME, AND POTENTIAL TREATMENT, ELUCIDATED[4]

Marfan Syndrome (MFS) is a genetic disorder of connective tissue with multi-systemic manifestations, which typically involve the skeletal, cardiovascular and ocular systems. It is associated with fibrillin-1 (FBN1) gene mutations, an extracellular matrix protein. The biggest risk for patients with Marfan syndrome is a ruptured aorta, which can kill them. Studies with animal models have helped in elucidation of the patho-physiologic mechanisms of the syndrome, the core role of transforming growth factor (TGF-β) signalling pathways in progression of aortic aneurysm and the promising role of the antihypertensive drug losartan in attenuation of aortic aneurysm by antagonising TGF-β signalling. In a recent mouse model, Dietz's group further explored the role of losartan in TGF-β signalling modification. A protein ERK (extracellular signal regulated kinase) which is aberrantly activated by TGF-β signalling is responsible for the causation of aortic aneurysm. Losartan efficiently blocks this ERK protein signal. A clinical trial enrolling 608 subjects, aimed at studying the efficacy of losartan over β blockers in preventing aneurysms in patients with Marfan syndrome is currently underway.

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13

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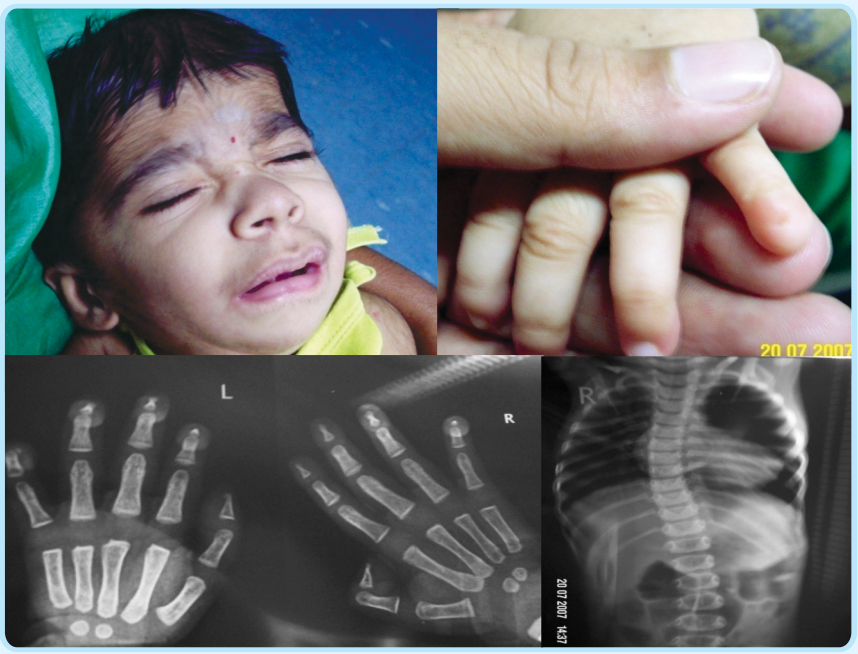
A one-year old female presented with global delay of milestones. See her face, fingers and radiographs for clues to identify this syndrome of mental retardation.



Answer to the PhotoQuiz 12 of the previous issue

Nail-Patella Syndrome (NPS) (OMIM# 161200)

Nail patella syndrome is caused by mutations in the gene LMX1B. It is inherited as an autosomal dominant disorder with variable expression. Clinically, NPS is suspected in presence of abnormalities of nail (aplasia, hypoplasia, ridging, triangular lunulae), patella (aplasia, hypoplasia) and iliac bones (horns, hypoplasia, flaring). Associated morbidity is mainly due to eye (glaucoma) and kidney involvement (nephropathy). Other organs may be involved, resulting in hearing impairment, gastrointestinal and neurological problems. Periodic evaluation is indicated for early detection and management.

Correct responses to PhotoQuiz No. 12 were given by

1. Sidramayya SS, Davangere
2. Vivekanand VV, Davangere
3. Yatheeshan KK, Kasaragod
4. Saminathan D, Trichy
5. Monika Sharma, New Delhi
6. Ravi Goyal, Kota
7. Anupama Bhave, via email
8. Mohandas Nair, Calicut
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