B D R News

The official newsletter of The Birth Defects Registry of India, (A Unit of Fetal Care Research Foundation)

Volume 3 Issue 3: July 2003

PROCEEDINGS OF THE BIRTH DEFECTS REGISTRY MEETING HELD ON THE 8TH AUGUST 2003.

8th August 2003 was an eventful day in the history of the Fetal Care Research Foundation (FCRF). The program for the day was scheduled in two sessions, with an inaugural function of a support group for MPS disorders and a symposium on Down's syndrome. Apart from CBDR members, a group of special children with their parents, staff members and student volunteers from Mathru Mandir and representatives from the media were present on that occasion. The guest speaker was Mrs. Rekha Ramachandran (President, Down's syndrome association Tamil nadu).The invitees were given a warm welcome by Dr. S. Suresh. He observed that we are moving a step forward towards realizing our goal of "supportive care" to those children affected with birth defects.

INAUGURATION OF MPS SOCIETY OF INDIA:

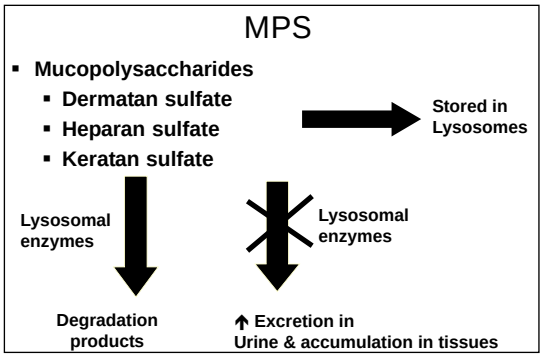
Dr. Suchitra Ravishankar gave a brief introduction about MPS to the audience, which was followed by the inaugural function.

It was heart-warming to see the special children light the kuthuvillaku to mark the inauguration of MPS society of India. The children were presented with mementos by Dr. Suresh & Dr. Sujatha Jagadeeesh. FCRF plans to meet the families periodically and organize activities like annual medical check-ups by various medical specialists and interact with other MPS societies abroad to access new developments in the treatment of MPS disorders. The parents were happy and optimistic about the benefits they would reap from the society.

AN INTRODUCTION TO MUCOPOLYSACCHARIDOSES (MPS)

Lecture by Dr. Suchitra Ravishankar (Associate Clinical Geneticist, Mediscan systems)

Mucopolysaccharidoses are a group of inherited **LYSOSOMAL STORAGE DISORDERS.** They occur due to the deficiency of certain lysosomal enzymes. Mucopolysaccharides are otherwise called Glycose Amino Glycans, polyanionic polymers (GAGs). These are alternating carbohydrate residues of N-actyl hexosamine & uronic acid. As they are major components of intercellular substances of connective tissues, bony changes are characteristic of MPS. The degree of disability and overall prognosis of each type depends on the physical and mental involvement.



Multiple enzymes are involved in the degradation of GAGs. Deficiency of just one of the enzyme causes this disorder.Many clinical features are common to all types of MPS. However these symptoms vary with the intensity of the disease. Incidence of this is said to be !/25000. All the types have autosomal recessive mode of inheritance except Hunter syndrome, which is an X-linked disorder.

Types of MPS:

· Hurler Syndrome MPS Type I
· Hurler Scheie Syndrome MPS Type I H/S
· Scheie Syndrome - MPS type IS
· Hunter Syndrome MPS Type II A&B
· Sanfilippo Syndrome MPS type III

A) Sanfilippo A - MPS type III A
B) Sanfilippo B - MPS Type III B
C) Sanfilippo C - MPS Type III C
D) Sanfilippo D - MPS Type III D

· Morquio Syndrome - MPS Type IV A& B
· Maroteuax- Lamy Syndrome - MPS Type VI
· Sly Syndrome - MPS Type VII 1,2,3 subtypes

Various Types Of MPS

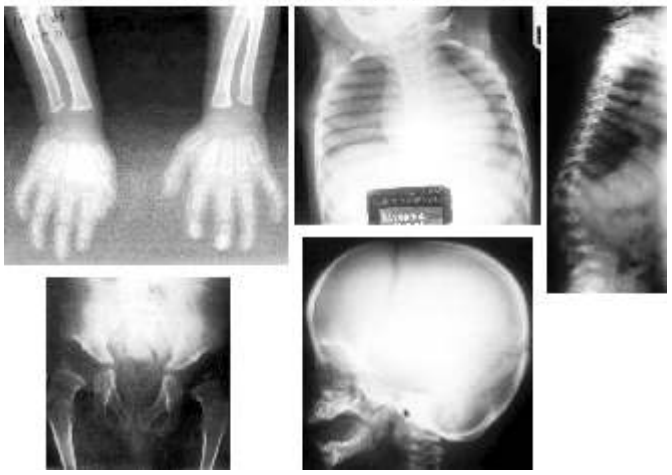
Short Stubby Beut Fingers

Among these, Hurler syndrome is the classic prototype of all MPS disorders. This is caused by the deficiency of enzyme alpha iduronidase and this may be present in three forms as

Hurler---Type I H
Scheie---TypeI IS
Hurler / Scheie---Type I/HS

In all these conditions there is excess accumulation and excretion of Dermatan & Heparan Sulfate due to enzyme deficiency. These children are normal at birth. As the GAGs accumulate, coarse facial features start appearing in the first year of life. The pathology behind is vacuolated gargoyle cells (lysosomes engorged with GAGs) in tissues , which in turn manifest in different ways in various systems. In the CNS there is thickening of meninges, hydrocephalus and peripheral nerve compression. In the skeletal system it presents as dysostosis multiplex causing rigidity and restricted movements of the limbs. In the CVS, there is thickening of cardiac valves and endocardium leading to aortic and mitral valve regurgitation, narrowing of coronary arteries and stiffening of the myocardium leading to congestive heart failure. Other common clinical features include, short stature, dysmorphic facies, dolicocephaly, frontal bossing, metopic sutures, prominent eyes, corneal clouding, depressed nasal bridge, broad nares, thick lips, enlarged tongue, gibbus, kyphoscoliosis, pectus carinatum, hepato spleenomegaly and umbilical hernia/inguinal hernia. Deafness and visual deficits may also be present. There may be a delay in milestones during infancy which would improve between 24 years of age and later deteriorate progressively. These children suffer from repeated respiratory infections and have difficulties in developing language skills due to macroglossia and auditory and visual deficits.

Radiological – Dysostosis Multiplex



Type IV MPS - Morquio syndrome is distinctly different from other forms in that odontoid hypoplasia is present in this condition.Type VII MPS - Sly Syndrome can present as hydrops fetalis in severe form.

Diagnosis & Treatment of MPS in done by clinical and radiological examination, biochemical assay and molecular studies. There are no specific drugs and treatment protocols for MPS. Recently a U.S based company has launched a drug for MPS I type - Aldurazyme, after extensive enzyme replacement therapy (ERT) trials. This is yet to be marketed to other countries. MPS support group hopes to access this drug for the benefit of our patients in future. BMT (bone marrow transplant) is occasionally resorted to for this disorder. Gene therapy at present is restricted to animal studies.

Genetic Counseling for the affected family facilitates confirmation of diagnosis of MPS in the index child by urine screening and enzyme assays in fibroblast culture. After confirmation recurrence risk is predicted for the siblings. Prenatal diagnosis is also offered by Chorionic Villi sampling (CVS) between 10 - 12 weeks of gestation for the parents assuring normalcy in subsequent pregnancies.

Mucolipidoses (MLS) are another group of storage disorders, which exhibit similar clinical features as MPS. These are caused by the deficiency of multiple hydrolases. Technically there is evidence of storage of both mucopolysaccharides and glycosphingolipids in various organs in MLS disorders. These are of 4 types. I-cell disease is the prototype of MLS. This is characterized by coarse facies, dysostosis multiplex and gingival hyperplasia.

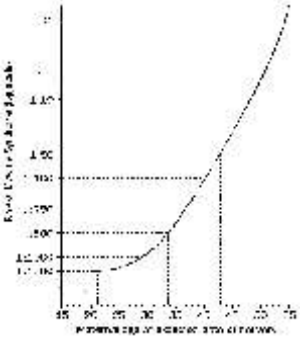
The excerpts of the presentations made in the II session on "HOLISTIC APPROACH TO DOWN SYNDROME BEFORE AND AFTER BIRTH" are furnished below.

AN INTRODUCTION TO DOWN'S SYNDROME, (DS), GENETIC COUNSELING AND PREVENTION OF DOWN'S SYNDROME

By Dr. Sujatha Jagadeesh (Clinical Geneticist, Mediscan systems)

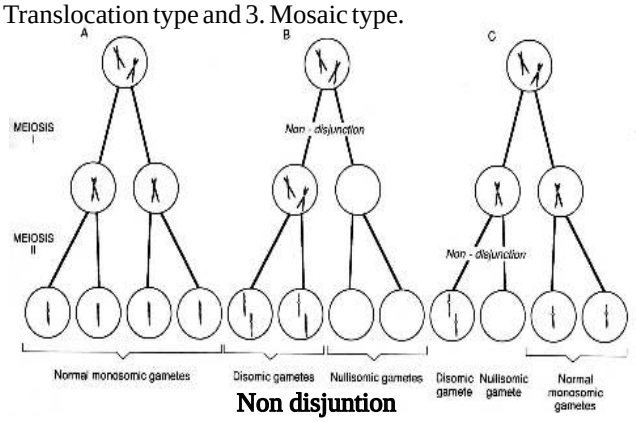
Dr. Sujatha Jagadeesh commenced her talk with an introduction to Down 's syndrome and she went on to elaborate genetic counseling for Down's and prevention of Down's syndrome.

The underlying cause of this non curable birth defect is an extra chromosome 21 present in the cells of the affected which is called Trisomy 21.She emphasized that it is a social problem as the occurrence of DS has a long term impact on the near family and the society at large. It is our responsibility to provide the best supportive care to these children as they have a reasonably good longivity. They are mentally challenged with varying degrees of comprehensive abilities.11% of the affected develop clinical dementia by 50 years and 66% by 60 years. They also suffer from associated cardiac and gastrointestinal abnormalities requiring supportive medical care. Nearly 58% have one major congenital anomaly. The two most frequently occurring anomalies are cardiac defects(45.8%) and gastrointestinal tract anomalies(11%). The common characteristic features of this condition would include flat occipit and facial profile, upslanted eyes, inner epicanthic folds, speckling of the iris, hypotonia, excess skin fold at the back of the neck, abnormal ears, curved 5th little finger, single palmar crease and sandal toe gap.



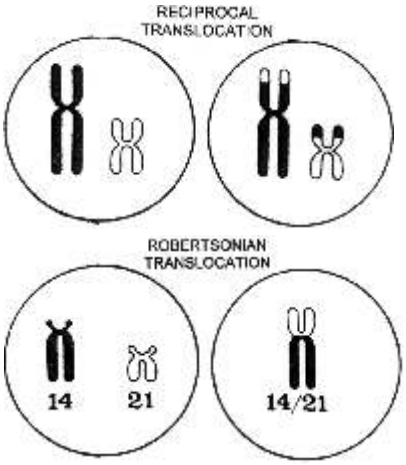
Incidence of DS range from 1/600 - 1/800. Maternal age contributes to the risk. As the maternal age advances there is higher risk for delivering babies with DS. <u>However 80% of the DS babies are born to mothers of younger age group as more number of conceptions occurs at this age.</u>

There are three types DS. 1.Non disjunction type 2. Translocation type and 3. Mosaic type.



Non disjuntion

Diagrammatic Representation of Translocation



In the mosaic type both normal cells and trisomy21 cells are found in the karyogram(Chromosomal arrangement) of the affected.

Genetic counseling for DS depends on the type of DS that has happened in the sibling or in the family. If the parents have had a previous child or a close relative with DS due to de-novo mutation as in non disjunction type, two types of tests are offered to them.

1. Direct test 2. Indirect test.

Indirect test: Triple screening test is offered as indirect test. Three maternal serum markers are analyzed in the blood sample of the mother between 16-20 weeks of pregnancy. The levels of MSAFP (maternal serum alpha feto protein), uE3(unconjugated estriol), HCG(human chorionic gonadotrophin) are the three serum markers analyzed. AFP is secreted by the liver, uE3 is secreted by fetal adrenal and processed in the fetal liver & placenta and HCG is a placental product. In the affected, the fetal products are lowered and the placental products are increased. Along with the three serum marker values, details regarding maternal age, LMP date, USG measurement of BPD (biparietal diameter) of the fetus and maternal weight are fed into a software to derive the TST results. The results are interpreted as either screen negative or screen positive. Screen negative means that the mother is at a lower risk for DS and screen positive subjects the mother to a higher risk for delivering a fetus with DS. However, the result screen positive warrants an invasive. test (direct test) to rule out this risk. To put it precisely, TST is not a YES or NO test to find out the presence and absence of DS in the fetus. It only helps to define or modify the mother's risk for aneuploidy. Other than TST, tests like Double Test and Quadruple Test are also available. In the double test, MSAFP and free beta HCG are assessed between 15 - 22 weeks of pregnancy. The detection rate is 60% with a FPR(false positive rate) of 5%. In the TST, the detection rate is between 60 - 70% with a FPR of 5%. In the Quadruple test, MSAFP, free beta HCG, uE3, and Inhibin are analyzed. Here, the levels of MSAFP and uE3 are lowered and the other two are elevated in the affected. This has a detection rate of 76% with a FPR of 5%.

First trimester screening has been introduced since 1997.This test takes into account the Nuchal Translucency measurement, PAPP (Pregnancy associated plasma protein) and free beta HCG to give results. This is done between 9 - 14 weeks of pregnancy. Compared to other modes of screening, this has a higher (85%) detection rate for a 5% FPR. ***Mediscan systems is shortly launching this test for screening Down syndrome.***

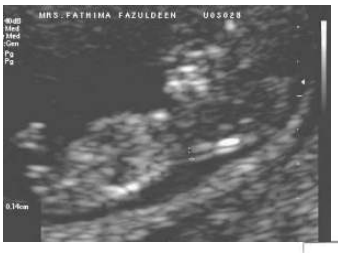
ANTENATAL DETECTION OF DOWN'S SYNDROME BY ULTRASOUND

By Dr. S. Suresh (Director, Mediscan systems)

While speaking on the role of USG in detecting Down's features in the fetus, Dr.Suresh said, that the markers for DS could be classified into two categories, biochemical and USG markers. Many ultrasound markers for chromosomal anomalies have been described in the II trimester. They are: nuchal thickness, hyperechoic bowel, echogenic intracardiac focus, short femur / humerus, pelviectasis, mild ventriculomegaly, clinodactyly, sandal gap, pericardial effusion, widened pelvic angle. The markers may be found in combination or isolated. The risk of Down's increases with the number of markers. Nuchal fold thickness >6mm in the II trimester is found to be an important marker which warrants an amniocentesis to rule out DS.

The two major markers in the first trimester are:

A. Increased Nuchal translucency
B. Presence or absence of the fetal nasal bone.

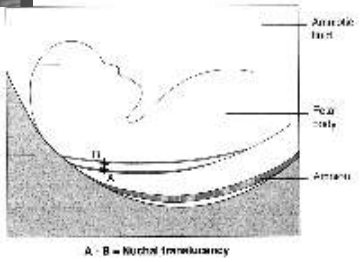


How to measure?

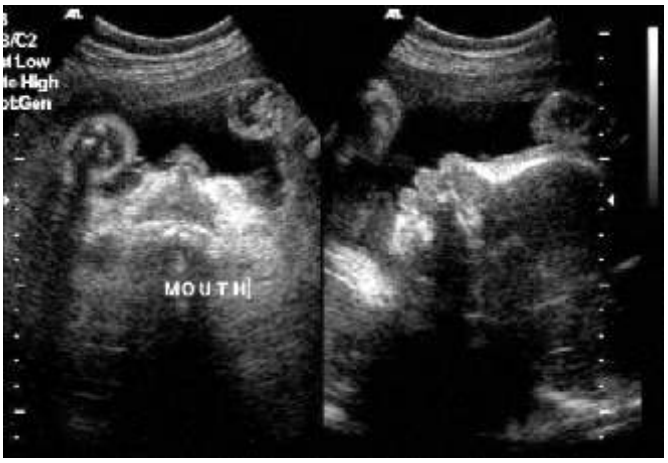
N- < 3mm

Nuchal Translucency

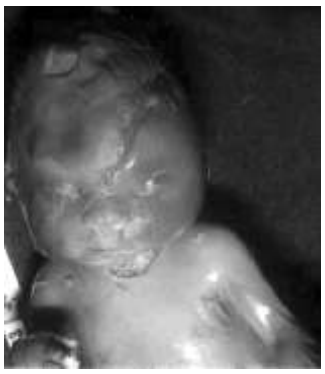
The right way to measure



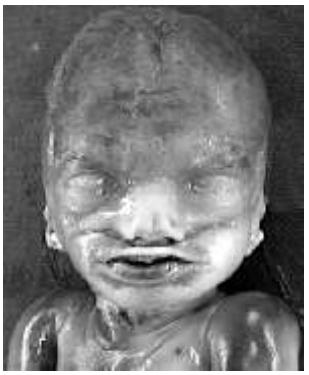
The available data on Nuchal translucency suggests that it should be included as part of I trimester Ultrasound (9-14 weeks).



The presence or absence of the fetal nasal bone has shown some promise to be a good marker. However, at present there are conflicting reports and larger data is required to validate the routine use of nasal bone as a marker. According to a study by Kypros Nicolaides, 701 fetuses in high risk women (advanced maternal age, screen positive) were scanned for the presence / absence of nasal bone between 11 - 14 weeks of gestation. CVS was done in these pregnancies, which revealed that 73% of the DS affected fetuses had absent nasal bone and it was absent in only 0.5% of normal fetuses. (Cisero S et al Lancer 2001) The main limitation of this study was that it was done on a high risk group and hence not applicable to low risk population.
Looking out for the characteristic facial features of DS by USG is also a difficult exercise and will not yield the expected results.



17 - 18 Weeks



20 - 21 Weeks

As shown in the picture both the affected fetuses do not exhibit clearly the down's features and only their karyotyping proved them to be affected. The reason for this could be, the characteristic features evolve over a period of time and cannot be easily made out in during gestational period.
Using the "genetic sonogram", the type of aneuploidy based on the presence or absence of USG markers and also the degree of risk can be estimated using likelihood ratios.

Dr. Suresh concluded his presentation saying that no marker whether biochemical or USG is 100% sensitive in picking up DS. The more is the number of parameters, the higher is the sensitivity of the screening tests. USG and biochemical markers in combination will reduce the number of invasive procedures. As already mentioned, current promise on screening for DS lies in combining the first & second trimester screening results and assessing the risk in the population.

COMPREHENSIVE CARE OF CHILDREN BORN WITH DOWN'S SYNDROME

Mrs. Rekha Ramachandran (President & Chiarman---Mathru Mandir(Down's syndrome association of Tamilnadu)

Dr. Indrani Suresh, while introducing Mrs Rekha Ramachandran, described her as a unique person who is toiling hard to preserve the dignity of those affected with Down's syndrome.

Mrs.Rekha commenced her talk on a touching note, that her speech is a mere oration and not a high tech power point presentation as she cannot project her emotions, neither the pain she experienced while bringing up her Down's child nor the happiness in raising her daughter who has blossomed into a fine personality today. The challenges she faced in grooming her daughter and the experiences she had in her quest to know everything about this disorder motivated her to start a support group for DS affected children so that all guidance were available for the affected families under one roof. She has gained wide knowledge and experience in handling and training the affected from support group organizations in the U.S and U.K. At Mathru Mandir today, she has more than 3000 affected families from all over India under her motherly care and attention.

While talking about comprehensive care of babies born with DS, Mrs. Rekha said that quality of life of the affected has greatly changed now with good supportive care who otherwise were considered to be mongoloids and useless. She insisted that supportive therapy for such children starts from 'Day One' of the neonatal period. Hence the responsibility falls on the obstetricians and pediatricians to identify the areas where the child requires supportive care and treatment. This requires continuous monitoring by the parents and medical personnel to facilitate better rehabilitation. Training these children needs enormous patience and perseverance on the part of parents and trainers. She said, that such efforts bring about rewarding experiences. She also emphasized that early intervention by strong visual, olfactory, auditory and tactile stimulations are very important to achieve results. These children are otherwise poor performers due to the underdeveloped neural cells of the brain, which do not respond to external stimuli. They are generally hypotonic; hence physiotherapy should be aimed at strengthening of muscles for the child to maintain balance. Early training of the infant to sit helps him/her develop head control. Teaching the child to creep and crawl by supporting the hips and chest will be useful exercises. Absence of training will lead them to methodically do wrong things all the time due to their impaired brain capacity.

When she talked about the nutritional needs, she quoted Dr. Warner, who has done extensive work on DS children. His nutritional metabolic

therapies with a drug called “Hap Caps” have yielded wonderful results among the children under his care especially those with hypothyroidism.. Hap cap is a compilation of vitamins, minerals, digestive enzymes, essential fatty acids and several drugs including thyroid hormones. Dr. Warner claims that children on this drug have improved I.Q levels and less chronic illnesses. He also recommends supplementation of omega-3 oils to maximize the effects of Hap caps which in turn promotes soft healthy skin, reduces inflamed tissues and improves immune response in DS children.

Mrs. Rekha proudly mentioned that with early intervention and thyroid monitoring, hundreds of her children are attending nursery school. A few years of schooling in normal nursery and primary school and later wholesome training in special school like Mathru Mandir will improve their potentials. Adolescence in DS is a challenging phase for the parents as in their other children. It brings in a lot of physical and emotional stress on them and they start exploring themselves. Hence it is essential that proper sex education be imparted to these children so that they do not become withdrawn or aggressive. This will also help them cope up with their pubertal developments. Contraceptives and sterilization may be opted by parents of children who fail to understand the implications of sexual activity. The best way to channelize their potentials is to enroll them in various activities like special sports, dance and other suitable vocational streams. Mrs. Rekha also heads the Special Olympics committee, which organizes sports for special children both at national and international levels. Recollecting her experiences with her daughter during her adolescence, Mrs. Rekha conveyed the message, that every single human being is different with his or her own personal needs and desires. Everyone has his / her own limitations and problems. By helping such teenagers to develop skills in as many areas as possible, parents and professionals are providing an education for life, which can be difficult even at best of times.

FOR REHABILITATION OF DOWN'S SYNDROME AFFECTED CHILDREN

CONTACT:
MRS. REKHA RAMACHANDRAN
 # 50 SRIMAN SRINIVASAN ROAD
ALWARPET, CHENNAI 600 018.
PHONE #S 24970824
RESIDENCE 2499 5224
MOBILE: 98410 99130

An appeal

Help a national cause Join the Birth defects registry. If you are already a member of the registry, please motivate a friend to become a member of the registry. If you are not a member kindly contact us. Let us work together to build a healthier nation.

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