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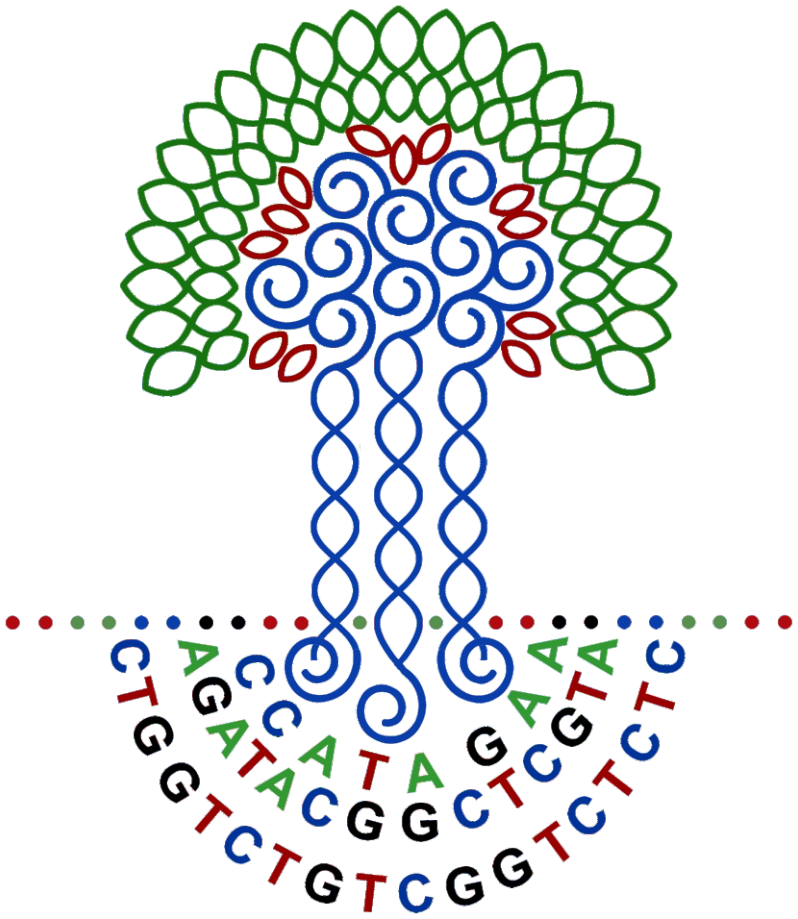

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PhotoQuiz - 60

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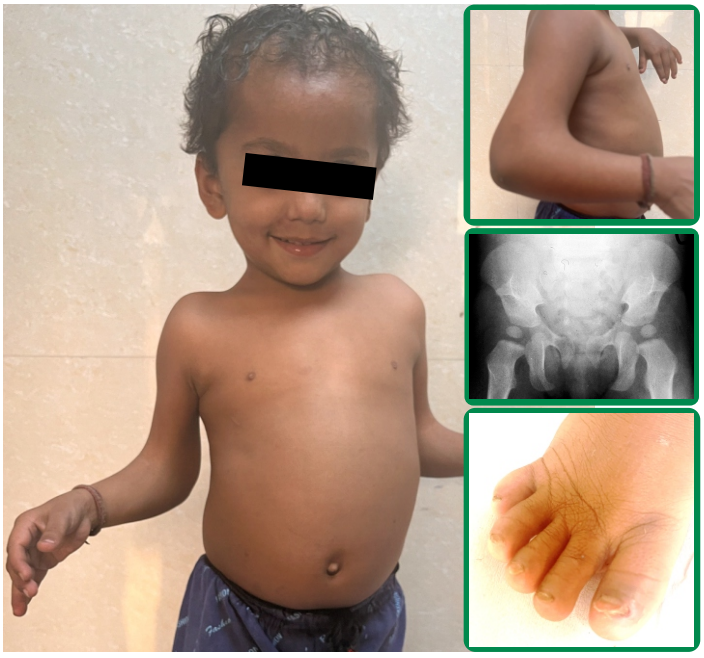
This three-year-old boy was referred for evaluation of elbow joint contractures. His mother died 6 months ago due to renal failure. Identify the condition.

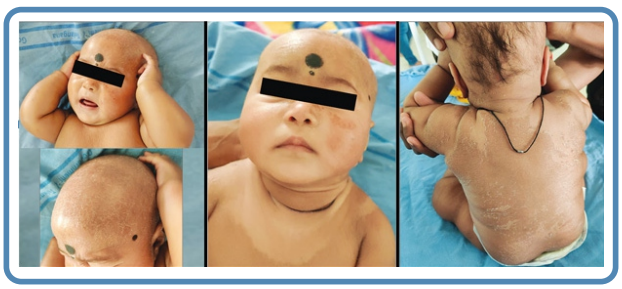
Please send your responses to editor@iamg.in
Or go to http://iamg.in/genetic_clinics/photoquiz_answers.php
to submit your answer.



Answer to PhotoQuiz 59

Biotinidase deficiency (OMIM #253260)

Biotinidase deficiency is an autosomal recessive inborn error of metabolism. Profound biotinidase deficiency is characterized by cutaneous manifestations such as alopecia, skin rash and candidiasis, and neurological abnormalities such as seizures, ataxia, developmental delay, muscle tone abnormalities, and visual and hearing deficits. Individuals with partial biotinidase deficiency may have milder manifestations such as skin rash, hair loss and hypotonia. Biotinidase deficiency is caused by biallelic variants in the *BTD* gene (*609019). Symptoms can be effectively controlled with daily lifelong high dose biotin supplementation. Presymptomatic detection through newborn screening and early initiation of biotin therapy can prevent disease manifestations.



List of correct responses to PhotoQuiz 59 provided on page 2.

GeNeDit

Care for the Rare: Steps in the Right Direction

Editorial

February 28th was celebrated across the world as Rare Disease Day. Many centres in India held events to commemorate this occasion. This has once again thrown the spotlight on rare diseases and the patients and families affected with them. There are around 7000 to 8000 rare diseases and around 80% of them are due to genetic causes. Though individually rare, these disorders collectively pose a huge health burden. In India alone, due to the large size of our population, the number of patients affected with rare diseases is estimated to be at least around 70 million. Majority of these disorders are lifelong conditions and cause significant disability, and affected individuals need supportive care and multidisciplinary management throughout life. Disease-specific therapies and disease course-altering treatments are available for some of the conditions, especially the inborn errors of metabolism, inborn errors of immunity, hematological disorders, and some neuromuscular disorders such as spinal muscular atrophy and Duchenne muscular dystrophy. However, the cost for many of these therapies remains prohibitively high. Recent initiatives by the government such as creation of the National Registry for Rare and Other Inherited Disorders (NRROID) by the Indian Council of Medical Research (ICMR), formulation of the National Policy for Rare Diseases 2021 (NPRD-2021) by the Ministry of Health and Family Welfare (MoHFW), Government of India, and the Unique Methods of Treatment and Management of Inherited Disorders (UMMID) initiative by the Department of Biotechnology (DBT), are commendable steps towards improving the diagnosis and treatment of these patients. The year 2023 began on a very positive note, with the MoHFW releasing grants for treatment of many patients with rare diseases under the Rasthriya Arogya Nidhi (RAN) financial assistance scheme, and inclusion of three more government medical institutes as centres of excellence (CoEs) for rare diseases to cater to the large population across India, taking the number of CoEs from eight to eleven.

Like the disorders treated by them, medical geneticists in India have been a rare (!) group of specialists. Until recently, only few centres had trained medical geneticists and even fewer offered specialized training in the field. The number of available trained medical professionals adequately equipped to handle the huge burden of rare disorders in the country has been dismally low. The scenario is fortunately changing for the better. More medical institutes and tertiary care hospitals are now setting up medical genetics units and departments and more centres are now offering training courses in clinical genetics compared to about a decade ago. Though these efforts are in the right direction, there is still a long way to go to create a sufficiently big workforce of clinicians in the country to manage patients with rare disorders. It is a matter of great pride for the Indian medical genetics fraternity that Professor IC Verma, one of the founding fathers of the specialty in India and patron of the Society for Indian Academy of Medical Genetics (SIAMG), has been conferred the Padma Shri award for the year 2023. Not only is this very inspiring and encouraging for the budding medical geneticists in the country, it will also help to bring greater recognition for the field and create more awareness about rare diseases in India, something that Professor Verma has striven for throughout his entire professional career.

One of the best strategies to reduce the burden of inherited disorders and birth defects is to perform preconception and prenatal screening, offer appropriate prenatal genetic testing to identify these disorders associated with significant mortality and morbidity, and terminate affected pregnancies to prevent the birth of affected babies. However, at times, overzealous prenatal screening and testing may lead to antenatal detection of conditions such as sex chromosome aneuploidies, which in many cases do not cause significant disabilities. This could cause a lot of emotional trauma to couples and lead to wrongful termination of pregnancies. These issues have

been addressed in the GeneFocus and GeneVista articles in this issue. As for all other medical techniques, one has to ensure that while offering genetic screening and testing, the first and foremost principle of 'primum non nocere' ('first, do no harm') is followed.

As always, we hope our readers find the articles included in this issue relevant and useful in their clinical practice.

Dr Prajnya Ranganath
Associate Editor
1st April, 2023

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4. Dr Ravneet Kaur, Motherhood Chaitanya Hospital, Chandigarh
5. Dr Meenakshi Lallar, Prime Imaging and Prenatal Diagnostics, Chandigarh
6. Dr Sangeeta Khatter, Jindal IVF Hospital, Chandigarh
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Clinical Vignette

Spinal Muscular Atrophy Beyond the SMN gene: New Learnings for Common Phenotypes

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Abstract

The most common cause of spinal muscular atrophy (SMA) is biallelic deletion of exon 7/8 of the *SMN1* gene. However, SMA can also be caused by variants in genes other than *SMN1* (non 5q-SMA). We describe a child with motor delay since infancy and progressive muscle weakness of the lower extremity due to non 5q-related spinal muscular atrophy.

Keywords: Non 5q-spinal muscular atrophy, *DYNC1H1*

Introduction

Spinal muscular atrophy (SMA) is a rare genetic disorder characterized by progressive degeneration of the anterior horn cells of the spinal cord leading to muscle weakness and atrophy. The commonest cause of SMA is biallelic deletion of exon 7/8 of *SMN1* gene located on 5q13. However, SMA can also be caused by pathogenic variants in genes other than *SMN1* (non 5q-SMA). We describe a 10-year-old girl with motor delay since infancy and progressive muscle weakness of the lower extremity due to non 5q-related spinal muscular atrophy.

Patient details

A 10-year-old girl, first child of a non-consanguineous marriage, was evaluated in the genetic clinic for infantile-onset progressive lower extremity weakness. Antenatal and perinatal history was unremarkable. Bilateral clubfoot was noted at birth. She came to medical attention in early childhood for delayed motor milestones (sitting at 1 year, standing with support at around 2 years, and walking at 2.5 years). The other developmental domains were age-appropriate. She also had high myopia with strabismus noted at 3 years. She had frequent falls and was unable to climb stairs, run, jump, or kick. On examination, the child was obese [body mass index (BMI) – 30.4 (+2.4 Z)] There was no facial dysmorphism. Her higher mental functions were normal. She had a waddling gait. The muscle bulk and tone in all four limbs were normal. There was symmetric weakness of hip flexion, extension, abduction, adduction, and knee flexion with relative sparing of knee extension and ankle flexion/extension. Gowers sign was positive and power in the upper extremities was normal. There was also truncal weakness with lumbar lordosis. Deep tendon reflexes were normal except for a depressed patellar reflex. Bilateral ankle contractures were present. There was laxity in bilateral wrist joints. Examination of other systems revealed no abnormality. A clinical diagnosis of limb girdle muscular dystrophy (LGMD) was considered in view of the progressive lower extremity and truncal weakness along with preserved reflexes.

Serum creatine phosphokinase (CPK) was 235 IU/L. Nerve conduction studies were normal. Electromyography revealed large-amplitude motor units in the tibialis anterior and quadriceps along with multiple myopathic motor units in the gastrocnemius, gluteal muscles, and upper limb muscles (deltoid and extensor digitorum communis). No fibrillations or positive sharp waves in any muscle groups were seen. Differential diagnosis included muscular dystrophies, congenital myopathies and myasthenic syndromes.

To address the genotypic heterogeneity for the provisional diagnosis of LGMD, whole exome sequencing was performed which identified a heterozygous missense variant NM_001376.5:

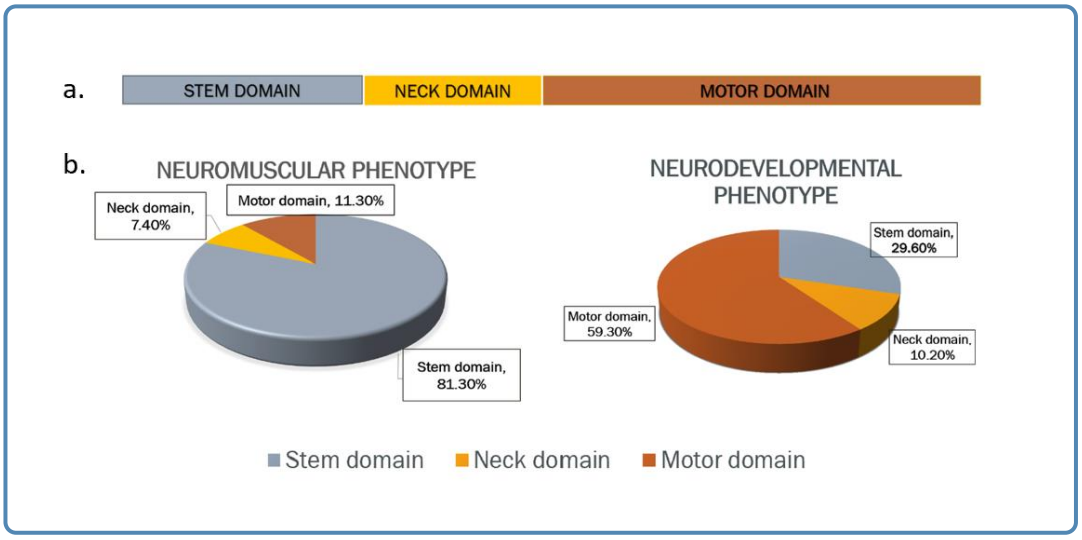

Figure 1 a. DYNC1H1 protein domains and associated *DYNC1H1*-related phenotypes. b. Pie-charts depicting the spectrum of *DYNC1H1*-related disorders. A predominant neuromuscular phenotype [spinal muscular atrophy (SMA)/Charcot-Marie-Tooth disease (CMT)/myopathy with or without central nervous system (CNS) features] is more commonly seen in mutations in the stem domain whereas predominant neurodevelopmental phenotype (intellectual disability (ID)/ autism spectrum disorder (ASD) with or without neuromuscular involvement) is seen in mutations in the motor domain. (Adapted from Amabile et al., 2020) .

c.752G>A (p.Arg251His) in exon 4 of *DYNC1H1*gene. The variant was validated with Sanger sequencing and parental studies showed the variant to be *de novo*. This variant has been previously reported in a patient with peripheral neuropathy (Antoniadi et al., 2015) as well as in patients with spinal muscular atrophy, lower extremity predominant-1 (SMA-LED1) but with a different amino acid substitution (p.Arg251Cys) (Chan et al., 2018) and not been reported in population databases. The in-silico prediction tools show that the variant is deleterious and is in the mutational hotspot. Hence, as per American College of Medical Genetics and Genomics/ Association for Molecular Pathology (ACMG/AMP) criteria, it is classified as 'likely pathogenic'. Based on the phenotype and molecular studies, the child was diagnosed to have spinal muscular atrophy, lower extremity predominant-1 (SMA-LED1).

Discussion

Chronic progressive lower limb muscle weakness is a common presenting feature in a variety of genetic disorders. Common differentials include muscular dystrophies, congenital myopathy, neuropathies, hereditary spastic paraplegia and spinal muscular atrophy. Some non-genetic causes of such presentations can be inflammatory myopathies, hypothyroidism, drugs and vitamin D deficiency which should always be ruled out prior to genetic testing.

SMA-LED1 is a rare motor neuron disease characterised by early-onset symmetric proximal lower limb weakness. Patients have a characteristic broad-based waddling-type gait, lumbar lordosis, feet deformities and joint contractures. Reflexes are normal except for a depressed patellar reflex in a few that differentiates it from 5q-linked SMA. The upper limbs are initially spared but might get involved later. Our patient also presented with this typical clinical profile. Muscle MRI shows atrophy and fat infiltration of the quadriceps femoris with hypertrophy of the semitendinosus and adductor magnus.

SMA-LED1 is caused by variants in the *DYNC1H1* gene (14q32.31) which codes for the cytoplasmic dynein complex heavy chain protein. This protein is involved in the intracellular transport of various proteins, organelles as well as organisation of the spindle pole. Disorders associated with *DYNC1H1* are all autosomal dominantly inherited and include Charcot-Marie-Tooth disease type 2O, Mental retardation-13, and SMA-LED1.

All the three *DYNC1H1*-related disorders show overlapping features in the form of sensorimotor neuropathy, lower limb weakness and central nervous system (CNS) involvement. A recent paper (Amabile et al., 2020) has suggested a novel classification system for the *DYNC1H1*-related disorders with those having predominant neuromuscular disorder (*DYNC1H1*-related NMD) as our patient, those having a combined NMD-CNS phenotype and those with a predominant neurodevelopmental disorder (*DYNC1H1*-related NDD). Patients with the neurodevelopmental phenotype may present with varying degrees of intellectual disability, learning disability, speech delay or global developmental delay. Neuroimaging can reveal brain abnormalities like ventriculomegaly, pachygyria, hypoplasia of the corpus callosum, pons or cerebellum. A few may develop epilepsy responsive to medications. Nerve conduction studies might sometimes indicate axonal impairment of the sensory or motor nerves. Extra-CNS manifestations like strabismus, amblyopia, congenital cataract, bicuspid aortic valve etc. have also been reported in them. A genotype-phenotype correlation has also been proposed with variants in the stem domain of the protein more likely resulting in a neuromuscular presentation and those in the motor domain more likely leading to a neurodevelopmental phenotype (Figure 1) (Amabile et al., 2020) Our patient has the variant in the stem domain consistent with an isolated neuromuscular presentation.

Conclusion

SMA-LED1 is an uncommon differential for spinal muscular atrophy with early onset, lower extremity predominant, progressive muscle weakness and preserved reflexes. A high index of suspicion is essential to consider this diagnosis.

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GeneEvent

Celebration of World Down Syndrome Day

'World Down Syndrome Day' was celebrated on 21st March 2023 at the Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow. The event included a panel discussion where individuals with Down syndrome participated as panelists and expressed their world views, and a fashion show where they 'walked the ramp' with grace and style.

GeneFocus

Prenatal Screening for Sex Chromosome Aneuploidies: Is it Justified?

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Abstract

Prenatal screening and testing for common genetic disorders and termination of affected pregnancies is widely accepted as one of the best strategies to reduce the burden of these disorders in the population. However, one has to consider the justification for doing prenatal screening for disorders which may be common but do not have significant disability associated with them. This article outlines the drawbacks of doing antenatal screening especially non-invasive prenatal screening (NIPS) for sex chromosome aneuploidies.

Key words: Non-invasive prenatal screening (NIPS), sex chromosome aneuploidies

Introduction

Non-invasive prenatal screening (NIPS) is a technical marvel and a revolution in screening for chromosomal disorders. Historically, Down syndrome due to trisomy 21 has been a prototype for antenatal screening and diagnosis. Starting from maternal age as the screening strategy, screening test has achieved more than 99% sensitivity and can be offered to all pregnant women (Gil et al., 2014). With use of next-generation sequencing based technology, NIPS achieved acceptance due to very high sensitivity as compared to other screening tests on mother's blood, namely double marker and quadruple marker screens usually done along with fetal ultrasonographic evaluation. Ease of testing and applicability at very early gestation are considered great advantages along with decreased need of invasive testing. The increased applicability resulted in the use of the test for other chromosomal aneuploidies including those of sex chromosomes and screening as early as 10 weeks of gestation. Superficially, this appears a win-win situation, though it is flouting the basic principles of population-based screening which are still applicable. A significant proportion of conceptuses with trisomy 21 are spontaneously aborted before 16 weeks and early screening test may detect them which is not necessary. Secondly, screening is usually done for common disorders while trisomy 13 and 18 are not common and being rare, the positive predictive value for these are significantly lower as compared to that for trisomy 21. Being usually lethal, the burden of these disorders is perceived relatively less as compared to that of rearing a child with trisomy 21 with lifelong disability due to mental handicap. Thirdly, NIPS includes sex chromosome aneuploidies, and guidelines by the American College of Medical Genetics and Genomics (ACMG) also strongly recommend this (Dungan et al., 2023). However, individuals with these disorders usually do not have major disability or significant morbidity.

It is time to ponder upon the recommendations and current practices of NIPS even if cost is not the issue. It may be an over-enthusiastic screening strategy for rare disorders like trisomy 13 and 18 and for sex chromosomal anomalies.

NIPS for sex chromosome aneuploidies

The most common sex chromosome aneuploidies are 45,X (Turner syndrome), 47,XXY (Klinefelter syndrome), 47,XYY (XYY syndrome), and 47,XXX, which have birth frequencies of approximately 1 in 2500, 1 in 500 to 1 in 1000, 1 in 850 to 1 in 3000, and 1 in 1000, respectively. As everyone knows, these are non-lethal abnormalities and there is no significant mental or physical handicap in most of them (Sait and Phadke, 2021). Most of the individuals with 47,XXX and 47,XYY will

go undetected throughout life. The reproductive issues in cases with 45,X and 47,XXY have solutions in this era of assisted reproductive techniques. Hence, these are not the candidates suitable for inclusion in antenatal screening test, as the only option after prenatal diagnosis is termination of the pregnancy. If detected in prenatal diagnosis by amniocentesis, there is a challenge for the genetic counsellor and dilemma for the family. But that is unavoidable and counselling should be positive. The available information about outcomes of 47,XXX and 47,XYY on the internet shows some increased prevalence of reproductive problems and behavioural problems, respectively. The families posed with such challenge have a lot of anxiety and may terminate the fetuses with such sex chromosomal abnormalities or may have issues with emotional bonding or difficulty while bringing up the child.

Though we say that nondirective counselling should be done and the decision of termination should be of the family, understanding the long term outcomes of such variations (without significant clinical abnormalities) is beyond the capacity of lay persons. Hence, prenatal screening for such common aneuploidies without grave significance should not be offered and aneuploidy of sex chromosomes should not be included, just because it is technically possible. The argument against this could be that we shall be failing to diagnose 45,X and 47,XXY. But even if these aneuploidies are detected in amniotic fluid karyotype/ microarray, we communicate that the possible problems are short stature, cardiac anomaly, hypogonadism, and infertility, all of which are manageable.

Prenatal screening is mostly done with the objective of prevention of the birth of a child with disability. Termination of pregnancies with isolated sex chromosomal abnormalities is not justified and hence screening tests should not include these. It leads to undue anxiety and unnecessary termination of pregnancies.

NIPS in the first trimester

The argument for first trimester NIPS is that it enables early reassurance for the pregnancy. But the primary objective of prenatal screening and diagnosis is to prevent the birth of a child with disability and lifelong burden associated with it and not reassurance. No prenatal test can give the assurance of a healthy baby. As half of trisomy 21, more than half of trisomy 13/ 18 and most of monosomy X are spontaneously aborted during the first trimester, it is advisable to do screening after the first trimester. Many of us have experienced that by the time the NIPS report comes as positive, USG already is showing hydrops or cystic hygroma in many cases. This leads to unnecessary guilt on the mother of taking the decision of aborting the pregnancy which was likely to get aborted on its own or at least would have got diagnosed in the antenatal ultrasonogram (USG) at around 13 to 14 weeks.

NIPS for other aneuploidies

Most fetuses with trisomy 13 and 18 have some USG-detectable anomalies and may be picked up simultaneously. Due to the rarity of these conditions, possibility of their getting detected by USG, and the low positive predictive values of screen positive cases, including trisomy 13 and trisomy 18 in the screening panel also needs reconsideration. The prevalence of other rare autosomal trisomies (RATs) being very low, the positive predictive values are too low to be included for screening in the low-risk population. A positive NIPS result creates undue anxiety, increases the need for invasive testing and poses a dilemma for the family. The comprehensive review by Lannoo et al. (2023) has tabulated all the information about predictive values for screening for RATs and various issues related to that. It is an eye-opener for clinicians and provides the list of research issues in this area.

The better option

It may be better to do NIPS only for trisomy 21 at 16 to 18 weeks of gestation and combine it with maternal serum alpha fetoprotein assay, which is still very important (Racusin et al., 2015; Siddesh et al., 2017) and ultrasonography for malformations. One-stop screening for genetic disorders antenatally should be convenient and not a burden. As NIPS is still too costly to be advocated for population-based strategy, quadruple/double marker screening followed by chromosomal analysis by cytogenetic microarray on amniotic fluid is a cost-effective strategy as it may miss some fetuses with trisomy 21 but will detect other chromosomal imbalances of clinical significance (Phadke et al., 2017).

Secondly, in the name of 'non-directive counselling' we should not create and pose dilemmas for the pregnant woman and let her face the difficult decision-making with her limited knowledge of medical disorders and ability to understand the complexities of uncertain outcomes. No amount of genetic counselling can give an accurate picture about the life of an adult with Klinefelter syndrome and Turner syndrome. During pregnancy the mother is emotionally labile and very sensitive about the baby in the womb. The screening programs should be such that the dilemmas in front of the family are minimal and the screening program should be only for the disorders for which we feel termination of the pregnancy is ethical.

Thirdly, as screening programs (with the good intention of improving outcome of the pregnancy) for genetic disorders, preeclampsia, etc. are increasing, they are causing an immense burden of the logistics of testing, providing appropriate pre and post-test counselling, understanding counselling issues, and facing uncertainties. Due to unavailability of genetic counsellors, involvement of social workers in counselling for prenatal screening, and the time constraints of the clinicians, the families usually do not get adequate and clear information during pre-test counselling. There are limited studies available in published literature documenting the magnitude of anxiety generated in the family due to prenatal screening, but all of us have the experience of seeing 'would-be mothers' scanning the internet at night and losing sleep over the screening test results. We have to see how to minimize the anxiety and try to keep the woman happy and cheerful during pregnancy. Outcome of most pregnancies is good, but it will not be incorrect to say that most of the pregnant women spend a significant time worrying about the possibility of chromosomal disorders.

Even those who refuse screening tests carry the burden of anxiety. In addition to improving pre-test counselling, as a medical genetics society we need to decide what to offer. The emotional burden of the tests for preventing disorders (very rare trisomy 18 and 13 and common sex chromosomal anomalies with satisfactory outcome) should not be more than the advantage of prevention. We need to carefully reconsider what we want to offer in screening tests. And last but not the least, research on the effect of screening tests on the emotional health of pregnant women is needed.

Conclusion

Prevention is better than cure. But in the case of prenatal screening the method of prevention of genetic disorders is termination of pregnancy. Though this option is justified and acceptable to many of us and the lay persons, wisdom and ethics should be the responsibility of the clinician who is offering the test. So, the medical genetics community has to take a decision about which disorders need to be included in the screening program. The severity of the disorder in terms of outcome and high prevalence should be points to consider while choosing the disorders to be included in NIPS. Hence, sex chromosomal abnormalities and trisomy 13/18 should not be included.

'We should not offer more and make the pregnant woman suffer!'

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GeNeViSTA

The Dichotomy of Medical Ethics in the Field of Fetal Medicine

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Abstract

Noninvasive prenatal screening (NIPS) by cell-free DNA (cfDNA) in maternal blood is increasingly being used for screening for common aneuploidies due to its high sensitivity and specificity. The increased uptake of this noninvasive test has also increased the prenatal detection of sex chromosome aneuploidies (SCA) which is usually an unexpected finding for parents and clinicians alike, especially when the ultrasound does not report any abnormal finding. One such condition being increasingly diagnosed prenatally is the triple X syndrome (47,XXX) which has a reported incidence of 1 in 1000. Since the outcome of this condition is highly variable, with a large majority thought to remain undiagnosed, counselling parents can be difficult for healthcare professionals. This paper highlights the challenges of providing non-directive, evidence-based counselling, the ethical dilemmas, and the contrasting outcomes depending on parents' choices when confronted with this unexpected diagnosis.

Keywords: Noninvasive prenatal screening, prenatal diagnosis, sex chromosome aneuploidy (SCA), triple X syndrome, 47XXX

Introduction

Noninvasive prenatal screening (NIPS) by cell-free DNA (cfDNA) in maternal blood is currently recommended as the best screening test for detection of the common aneuploidies in both singleton and twin pregnancies (Dungan et al., 2023). The increased uptake of this noninvasive test has also increased the prenatal detection of sex chromosome aneuploidies (SCA) that are reported to affect 1 in 400 newborns making these the most common chromosomal abnormalities (Hui et al., 2023). One such condition is the triple X syndrome (47,XXX) which has a reported incidence of 1 in 1000 in the general population. Triple X can be associated with orofacial clefts, cardiac abnormalities, and clubfoot which are usually detectable at prenatal ultrasound. In the absence of congenital abnormalities, triple X fetuses are not known to be at increased risk of other antenatal or postnatal complications compared to the general population, and women who opt to continue their pregnancies should receive standard obstetric care (Reimers et al., 2023).

Individuals with triple X are reported to be at increased risk of developmental delay, learning disabilities, and mental health disorders as compared to the general population, but these findings are variable and not present in every case (Tartaglia et al., 2020). There is also a difference in outcomes of prenatal versus postnatal diagnoses, with Wigby et al suggesting that children diagnosed with triple X prenatally may have a higher intelligence quotient (IQ) and adaptive skills though the risk for speech delay or learning disability still remains. However, accurate counselling regarding expected outcomes is difficult because only 10% of affected triple X individuals are ever clinically diagnosed (Wigby et al., 2016). A recent publication states that the reported data on medical and neurodevelopmental differences in individuals with triple X syndrome should be interpreted with caution because of the ascertainment bias that would be inherent to a condition that is diagnosed in only 10% of cases (Reimers et al., 2023). Since the outcome of this condition is highly variable, counselling parents can be difficult for healthcare professionals (Fisher et al., 2023). This paper aims to highlight this ethical conundrum by presenting three clinically similar cases that had different outcomes, thus highlighting the divergent ethical ramifications of these unexpected diagnoses.

Patient 1: A 36-year-old G3P1 with no live issue (first miscarriage, second unexplained intrauterine

fetal demise at 26 weeks gestation) consulted us in her third pregnancy for the isolated finding of aberrant right subclavian artery (ARSA) at the anomaly scan. Her triple marker showed low risk for Down syndrome. The options of noninvasive prenatal screening (NIPS) and diagnostic test, i.e. amniocentesis were discussed with the couple. The couple was counselled that NIPS remains a screening test despite its high detection rate and that a high-risk report will need confirmation with amniocentesis. Considering the bad obstetric history and the 1% risk of miscarriage associated with invasive testing, the couple opted for NIPS. NIPS reported 'low risk' for trisomy 21,18, and 13 but gave 'high risk' for triple X (XXX). The result was discussed with the couple, and they were offered amniocentesis. The couple was also given relevant clinical information regarding triple X (https://rarediseases.org/rare-diseases/trisomy-x/). After counselling, the couple opted against invasive testing as they felt they were okay to have a baby with triple X. They opted to do their karyotypes, and interestingly, the mother herself had a triple X karyotype. She went on to have a normal delivery of a healthy baby girl at term.

Patient 2*:* A 42-year-old primigravida who conceived naturally came to us at 14 weeks and 3 days with a high risk for Down syndrome on dual marker test. The risk was in the screen positive range (cut off of 1 in 250 used to define 'high risk') but it was actually reduced compared to the age-related background risk. An ultrasound was performed, and there were no structural abnormalities nor any markers for chromosomal abnormalities detectable at that gestation. The options of noninvasive prenatal screening (NIPS) vis a vis invasive testing, i.e., amniocentesis were discussed with the couple. This couple was also counselled that NIPS remains a screening test, and a high-risk result will need confirmation with amniocentesis. NIPS can be done at any gestational age between 9-24 weeks, whereas amniocentesis is best performed at or after 16 weeks. The couple opted for NIPS which was given the same day. The NIPS report came eight days later and reported 'low risk' for trisomy 21,18, and 13 but gave 'high risk' for triple X (XXX). The report was shared with the couple, and they were asked to come back for a consultation. The patient requested our team to speak to her sister, who happened to be a genetic counsellor, and we discussed this result with her. Since the positive predictive value of NIPS for sex chromosomal abnormalities is only about 50% (Kornman et al., 2018), amniocentesis was offered. The couple was agreeable, and an uneventful procedure was done the same day. The quantitative fluorescent polymerase chain reaction (QFPCR) report also reported triple X in the fetus. The couple was asked to consult the medical geneticist soon after the reports came. The expectant mother came for the consultation accompanied by her sister and was counselled regarding the possible outcomes of this condition. A non-directive counselling was done, and recent literature was shared with the mother. The mother and her sister expressed their wish to continue the pregnancy as she had conceived with difficulty. A day after this consultation, we started receiving disturbing, lengthy emails, calls and WhatsApp messages from the patient's husband accusing us of encouraging his wife to have an 'abnormal' baby. He was outraged at how could a consultation be done for his wife with his sister-in-law in his absence. This was when we realized that there was a difference of opinion between the couple regarding the continuation of pregnancy. We replied to the first mail addressing his concerns, and we reiterated that as clinicians, we could only provide correct information. Prompt genetic counselling was provided as soon as the diagnosis was confirmed. The decision to continue (or discontinue) the pregnancy is a prerogative of the couple, and we as clinicians would provide support in whatever decision they take. The husband sent a legal notice to his wife with a copy to our team that he will not be responsible for the upkeep of the 'abnormal' baby if she continued with the pregnancy. Eventually, the patient wrote a mail to the hospital administration that the fetal medicine team had spoken to her sister at her request and that she had no complaint regarding the clinicians dealing with her case. The hospital administration requested the husband to come for a meeting in which it was conveyed to him that an internal inquiry of the hospital did not find any 'malpractice' in handling this case. The couple filed for mutual divorce and the expectant mother chose to carry on with her antenatal care in another place.

Patient 3: A 39-year-old G3A2 came for a fetal medicine consultation at ten weeks gestation as she herself was diagnosed with a triple X karyotype on undergoing investigations for her previous two miscarriages. This lady has a postgraduate degree and is working at a senior position in a multinational company and has no history

of any significant medical or surgical history. The possibility of having a fetus with normal karyotype, triple X karyotype or XXY was discussed with the couple. Both parents were unanimous in their opinion that they would continue with the pregnancy in case the fetus turned out to have a triple X karyotype. An amniocentesis was performed at 17 weeks, and the fetal karyotype was normal. She went on to have a normal delivery of a healthy baby boy at term.

Discussion

It is difficult to define what constitutes 'ethics'. A combination of one's values, belief systems, and experience(s) shapes every individual's unique code of ethics. Society, in general, gives us a broad background of what constitutes 'right', but there remains plenty of room for variation within this framework. Fetal medicine is a particularly vulnerable branch as it deals with something that is partly unknown. An ultrasound done halfway through pregnancy at around 18-20 weeks is expected to predict how the fetus will evolve over the next 20 weeks and presumably even for the first two years after birth. Subtle findings or the so-called 'soft markers' generate a lot of anxiety when mentioned to expecting parents. As per standard clinical guidelines and recommendations, a fetal medicine specialist is expected to look for these and discuss the uncertainty of 'screening tests' vis a vis the certainty of diagnostic but invasive tests with an inherent albeit small risk of miscarriage (ACOG Practice Bulletin; 2020). Thus, the fetal medicine specialist walks a tightrope between flagging up findings and not alarming the parents enough to make pregnancy an arduous journey.

Add to it the recognition of newer findings where the outcome is highly variable. This dilemma was presented strikingly in these three cases where there was no 'structural' abnormality in the fetus but we, both the clinicians and parents, were faced with a diagnosis with no certain answers. These cases with similar test results also illustrate the dramatically different 'ethical' repercussions despite our best intentions of providing the most up-to-date, accurate information to parents in a timely manner and with nondirective counselling. We believe that there is no 'correct' way of dealing with these sensitive issues, and as clinicians, one can only take solace in the fact that one acted to the best of their capabilities and as per current guidelines. But does that absolve us from the upheaval that we create in our patients' lives, however unintentional that might be? The purpose of sharing these cases with the medical fraternity is to sensitize our colleagues to the vagaries of this specialty that has more unknowns than knowns.

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GeNeXpreSS

Next-Generation Sequencing in Newborn Screening

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Interpretation of Genomic Sequencing results in healthy and ill newborns: results from the BabySeq project (Ceyhan-Birsoy et al., 2019)

A randomized prospective pilot clinical trial was conducted (BabySeq Project) to investigate the clinical, psychological, and financial impact of nGS (Newborn Genomic Sequencing). This project analyzed childhood-onset and actionable adult-onset disease risk, carrier status, and pharmacogenomic variants in 159 newborns using nGS.

The study revealed that 15/159 newborns (9.4%) had a risk of childhood-onset diseases, none of which were anticipated based on the infant's known clinical or family histories. The data revealed that 3/85 newborns (3.5%) had an actionable adult-onset disease. Carrier status was established for recessive diseases in 88% and pharmacogenomics variants were reported in 5% of newborns. This study, hence, corroborates the utility of nGS in efficiently identifying the risk and carrier status for several disorders that the current newborn screening assays are unable to predict.

Application of a next–generation sequencing (NGS) panel in newborn screening (NBS) efficiently identifies inborn disorders of neonates (Huang et al., 2022)

A newborn genetic sequencing panel based on multiplex PCR and NGS was utilized to analyze 134 genes of 74 inborn disorders. This panel was validated in 287 samples with previously known mutations. The panel was able to identify 154 variants from 287 samples with 100% accuracy. A retrospective cohort of 4,986 newborns was analyzed using this panel and the results were compared with their biochemical reports. Of these, 113 newborns were detected with biallelic/hemizygous mutations. Within these 113 newborns, 36 were positive for the same disorder by both newborn genetic sequencing panel and conventional NBS (C-NBS). This investigation revealed that NGS combined with C-NBS can provide early and accurate detection of inborn disorders in neonates.

Newborn screening with targeted sequencing: a multicenter investigation and a pilot clinical study in China (Hao et al., 2022)

A panel of 465 causative genes for 596 early-onset, relatively high incidence, and potentially actionable severe inherited conditions was formulated for the Newborn Screening with Targeted Sequencing (NESTS) program in China. A cohort of 11,484 babies was screened retrospectively from eight Women's and Children's hospitals. The estimated clinical diagnosis rate in the program was observed to be ~95% on average. NESTS was executed in a hospital to screen 3,923 newborns to assess its clinical application, turn-around-time, feasibility, and cost effectiveness of making it a potential first-tier NBS program.

The role of exome sequencing in newborn screening for inborn errors of metabolism (Adhikari et al., 2020)

This study represents the largest-to-date sequencing analysis of 4.5 million infants born in California between mid-2005 and 2013 and of some infants who screened positive for tandem mass spectrometry (MS/MS) but were unaffected upon follow-up testing. Conventionally, MS/MS

had been performed for these infants to assess the presence of an inborn error of metabolism (IEM) but in the NBSeq (Newborn Sequencing) project, whole exome sequencing (WES) was done on the archived blood samples to evaluate it as an innovative strategy for NBS. The MS/MS has an overall sensitivity and specificity of 99.0% and 99.8%, whereas the WES has 88% and 98.4% respectively. A noteworthy point was that MS/MS had a low positive predictive value and outcomes were non-specific as well. Conclusively, the authors suggest that WES could become a secondary test for infants with an abnormal MS/MS as it could then decrease false positive results, facilitate punctual case resolution, and in specific cases, direct toward a more appropriate diagnosis.

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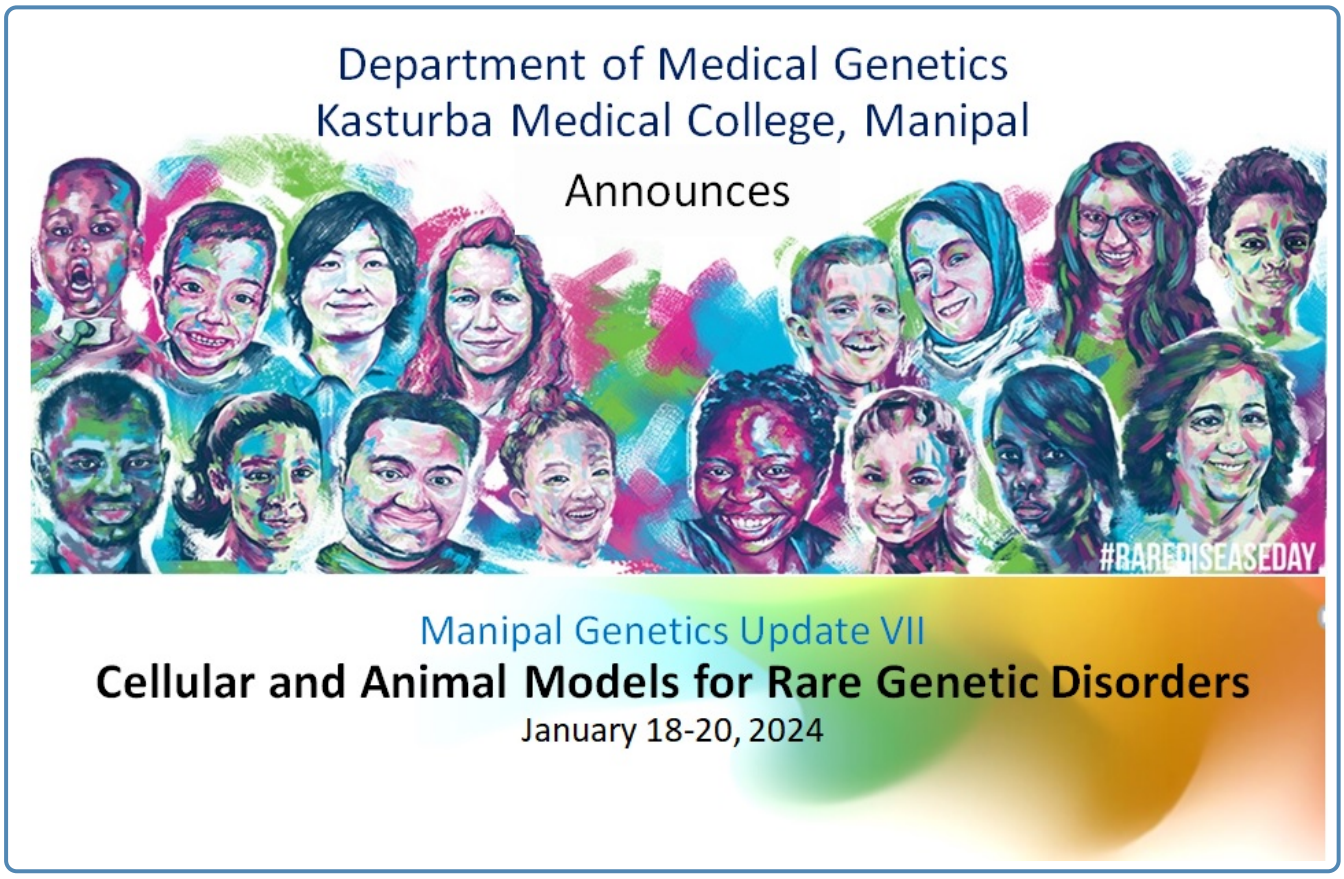

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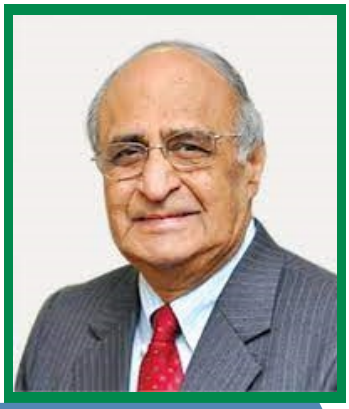


Professor I C Verma

Professor Ishwar Chander Verma, Advisor at the Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi, has been conferred the Padma Shri award for the year 2023. The fourth highest civilian honour in the country has been awarded to him in recognition of his immense contribution and tireless work in the field of medical genetics and rare diseases. Professor Verma is one of the founding fathers of medical genetics in India and a patron of the Society for Indian Academy of Medical Genetics (SIAMG). The award is a matter of great pride for the entire medical genetics fraternity of the country. The SIAMG family congratulates Professor I C Verma on this remarkable achievement and expresses its gratitude to him for his constant guidance and support.

Messages

My association with Professor I C Verma dates back to 1992 when I joined AIIMS, New Delhi as a "genetics-naïve pediatrician". I feel privileged, proud, and blessed for having him as my mentor and guru till date. Not only me, for the whole medical genetics fraternity in India, he has been the driving force for improving genetic services and research.

We are all aware about his illustrious carrier and academic achievements. A teacher par excellence, each of his talks will give you a new message and insight to ponder. And above all, he is an amazing human being.

I learnt several other things from Sir and tried to follow at least some and would like to pass on those for the young doctors and researchers:

- be passionate and enjoy the work you are doing
- get out of your comfort zone
- go an extra mile for helping patients and their families
- go an extra mile to build rapport with your colleagues and enjoy working together; you can never work alone
- remain inquisitive like a child and try to learn from everyone
- be updated about the research, what is happening in your work area and beyond too.

Heartiest congratulations Sir for receiving the well-deserved prestigious Padma Shri award which has made the whole pediatric and medical genetics fraternity proud. Wishing you good health and happiness always! We shall continue to seek your guidance and blessings.

Dr Madhulika Kabra
Professor, Division of Genetics, Department of Pediatrics,
All India Institute of Medical Sciences (AIIMS), New Delhi, India

Felicitation

Professor Verma did his premedical training at Elphinstone College, Mumbai and obtained MBBS at Amritsar Medical College where he was awarded the PN Chuttani Gold Medal for standing first in Clinical Medicine. He obtained MRCP London and DCH of Glasgow University in 1996. He is the first student to be bestowed MNAMS from the National Academy of Medical Sciences (NAMS) by examination. He received training in genetics in Zurich, London, Edinburgh, Manchester, Boston and National Institutes of Health (NIH), USA. He was awarded the Dr BC Roy National award for his role in establishing genetic services in India. In his brilliant academic career, he has more than 445 research publications to his credit. He established two genetic departments, the first one in India at the All India Institute of Medical Sciences (AIIMS), New Delhi in 1968 and in Sir Ganga Ram Hospital (SGRH) in 1997. He has been adviser to the Government of India and the South-East Asia Regional Office (SEARO) of the World Health Organization (WHO), and has received numerous awards.

It is a privilege and honour to pen musings of twenty years spent under the tutelage of Dr I C Verma. My entry into genetics was a chance event, and so was the opportunity to work in the department he created and nurtured at SGRH. First encounters with him are always "what can you do"? That is his uncanny ability to delve for new opportunities, recognize novelty in what comes along and put that to practice. He was always impatient to implement the latest technology, believing that diagnostic testing must be available in India for our patients. And he successfully achieved this at both centres established by him, AIIMS and SGRH.

He reads extensively and always reiterates the importance of being updated. His favourites are the New England Journal of Medicine, The Lancet, and the BMJ. He always had something new to tell us. It was a ritual in the department to discuss most cases of the previous day, and this enabled learnings for everyone in the department. He encouraged to publish, and while each manuscript went through innumerable edits, it taught the art of writing to highlight the novelty in the research. He is very hardworking and a perfectionist, encouraging youngsters and providing opportunities for newer vistas. He always had so much to accomplish in the limited hours of the day, but despite that, he was involved in each activity, including being informed of the spouses and children of his colleagues.

He has been a major influence and inspiration, and as I reflect, many instances "flash upon that inward eye". We are indebted to his passion, vision, and guidance and look up to him to this day for charting the path forward.

Many congratulations Sir for being awarded the Padma Shri and we are privileged to have learned from you and been guided by you. We wish you the best always!

Dr Ratna Dua Puri
Professor in Genetics, GRIPMER & Chairperson, Institute of Medical Genetics & Genomics, Sir Ganga Ram Hospital, New Delhi, India

Dr Verma Sir has been an inspiration to all and a great distant mentor to many of us. From the establishment of India's first division of Clinical Genetics to tribal and community genetics research, his journey at AIIMS has been inspiring. His exemplary clinical and research work, inquisitiveness to remain updated and learn about new technologies and therapies, excellent suggestions, continued participation in online meetings, and impactful lectures have always motivated me. I consider myself fortunate to be associated with the Genetics division at AIIMS, which he founded. Thank you Sir for always guiding us and heartiest congratulations on this stupendous achievement. Wish you a very healthy and peaceful life ahead.

Dr Neerja Gupta
Additional Professor, Division of Genetics, Department of Pediatrics, All India Institute of Medical Sciences (AIIMS), New Delhi, India

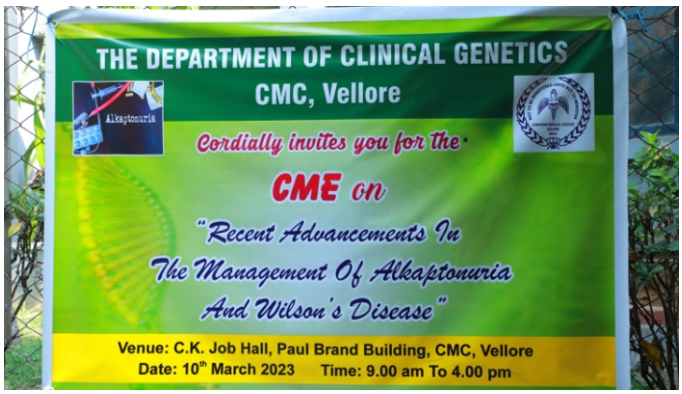
Rare Disease Day Events Across India

Rare Disease Day celebrations at the All India Institute of Medical Sciences (AIIMS), New Delhi on 28th February 2023; organized by the Ministry of Health and Family Welfare (MoHFW), Government of India, in association with the Central Health Education Bureau (CHEB), Division of Genetics, Department of Pediatrics, AIIMS, New Delhi and Maulana Azad Medical College (MAMC), New Delhi.

Rare Disease Day meet held at the Nizam's Institute of Medical Sciences (NIMS), Hyderabad on 11th March 2023; organized by the Lysosomal Storage Disorders Support Society (LSDSS), the Department of Medical Genetics, NIMS and the Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad.

Race for 7 held on 12th March 2023 in New Delhi; organized by the Organization for Rare Diseases India (ORDI) and the Division of Genetics, Department of Pediatrics, AIIMS, New Delhi.

Rare Disease Day event held on 28th February 2023 at Government Medical College, Thiruvananthapuram (GMCT); organized by the Genetic Division, Department of Pediatrics, SAT hospital, GMCT in association with LSDSS and the Cure SMA foundation.



Rare Disease Day-related CME on 'Recent Advances in the Management of Alkaptonuria and Wilson's Disease' was held on 10th March 2023 at Christian Medical College (CMC), Vellore; organized by the Department of Clinical Genetics, CMC, Vellore.

Race for 7 held on 19th March 2023 in Hyderabad; organized by the Organization for Rare Diseases India (ORDI).

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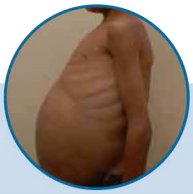

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