high index of suspicion so as to pick-up more subtle symptoms and signs suggestive of possible genetic causes. Preventive genetic evaluation should begin right from birth till the old age!

### Neonatal Period

Along with usual neonatal evaluation for well being of the newborn, we must look for subtle signs and symptoms of chromosomal, monogenic and metabolic disorders. This should follow necessary investigations and management. It is also essential to screen all newborns for Inborn Errors of Metabolism by day three/four of life. It is possible to screen for a large number of such disorders fairly quickly and accurately, which will help in the identification of children at risk so that medical interventions like pharmacotherapy, specific diets, etc. can be instituted so as to avoid deleterious effects on the physical and mental development of the child and preserve quality of life whenever possible. As incidence of many of these disorders is quite low and varies in different ethnic, geographical sub-groups it is necessary to identify the target disorders by epidemiological studies before finalising such screening programs. (*refer to* Chapter 8).

### Adolescent Period

This period is vital as it involves individuals who are more receptive to new ideas and suggestions, who will be the future parents. Inclusion of genetic evaluation and screening along with sex education, nutritional advice and contraception will be helpful in imparting awareness about genetic factors in healthcare, which will help them in seeking timely advice from their clinicians at the appropriate time. Secondary schools, colleges and youth organisations should be encouraged to actively participate in this campaign.

### Premarital Stage

Detailed history, thorough examination, follow-up testing done at this stage will certainly go a long way in preventing quite a few genetic disorders. Important areas to be covered are given in Table 1.4.

**Table 1.4**: Premarital evaluation

- Family/ethnic history of genetic disorder,
- Chromosomal abnormalities in either partners,
- Blood group incompatibility like Rh, hemoglobinopathy
- Familial cancers, coronary heart disease
- Reproductive tract anomalies in either partners,
- Occupational hazards

History of genetic disorders like thalassemia, haemophilia, muscular dystrophy, etc. will immediately prompt the clinician to advice appropriate screening tests to both partners so as to advice them about risk of recurrence, specific tests for prenatal diagnosis and management.

Although most of the conceptions with chromosomal defects are lost during antenatal stage, 0.6–0.8% of live born show chromosomal defects. Of these 0.4% are severe defects diagnosable at birth while 0.3% can be more subtle and have effect on child bearing. It is essential to have appropriate cytogenetic tests to be done in such individuals and counsel them accordingly.[4]

Blood group testing is now universally done in antenatal period but it should be done routinely at premarital stage itself. As it will give timely information in discordant couples so that necessary preventive measures can be taken up.

Certain cancers are caused by specific defective genes like BRCA-1 gene which is responsible for breast cancers. Cancers of breast, ovaries, colon and prostate are known to occur in families with presence of such abnormal genes. Some of the genetic disorders are more prone to cancers like leukaemia in Down's syndrome babies, Fanconi anaemia while gonadal malignancies are more likely in undescended testes and residual gonads in Turner's syndrome (*refer to* Chapter 16 for further details).

90%.[9] For achieving this spectacular success nuchal translucency measurement has to be accurately done on a high resolution scanner by a trained operator and software for risk assessment has to be used as well. With additional USG markers of nasal bone and Doppler flow studies of ductus venosus the detection rate can be further improved.

Recently a valuable addition in first trimester screening at has come 11–14th week, called "Advanced Double Marker" or "Penta Test". IN this there are 5 serum markers, PAPP-A, free beta hCG, placental growth factor (PGLF), AFP, dimeric Inhibin A. Addition of last three markers gives ability to screen for early onset PIH, NTD in addition to aneuploidy screening. Alone, this test has 86% DR at 5%false positivity for Tri 21. This is of significanc in situations where reliable NT measurements may not be available. With addition of NT, NB and DV markers, the DR reaches 98% at 5% FP for Tri 21, this almost reaches the sensitivity of NIPS!!!.[10]

The author set-up combined first trimester screening program in Mumbai city in 2002 analysis of first 300 tests showed a detection rate of 85% at 5% false positivity. Out of these, 22 cases were screen positive. After post-test counseling 18 underwent fetal tissue sampling and karyotyping, ten had normal karyotype while 3 showed aneuploidy (Tri21:2, Tri18:1).[11] To improve the detection rate sequential screening of 11–14 weeks combined testing followed by a quadruple test at 16–18 weeks has been tried with some improvements (DR 92%) (*refer to* chapter "Maternal Serum Screening").

It is now a well-accepted fact that first trimester combine screening (FTS) is a superior and early screening protocol as compared to second trimester screening tests. Early pick up of high risk cases at 11–14 weeks makes corrective measures like low dose aspirin, low molecular heparin therapy to be started when the vascular modulation of spiral arterioles has started beyond 12th week. Hence clinicians must encourage early reporting for first trimester screening. Second trimester screening should be considered only when patient has reported late, after 14 weeks or could not be performed.

*Chorion villous sampling* for confirmation in screen positive cases has emerged as the logical choice. The chorionic tissue is suitable for cytogenetic tests, DNA testing as well as metabolic studies. Though Amniocentesis is the most commonly performed prenatal diagnostic procedure CVS has the advantage of early and rapid diagnosis in first trimester thus reducing anxiety, keeping the pregnancy private and also to offer the safer first trimester termination option. To achieve the high safety and success of CVS it is essential to have properly trained operator with experience of at least 300–400 tests and should be well-versed in embryology and first trimester USG. Good resolution ultrasound machines also make the procedure quick and safe. Major clinical experiences in first trimester CVS are given in Table 1.5.

**Table 1.5:** Clinical experience of CVS

| *Sl. No.* | *Author* | *Technique* | *No of cases* | *Gest wk* | *Success%* | *Preg loss%* |
|---|---|---|---|---|---|---|
| 1. | Brambati, *et al.* | TC | 1305 | 8–12 | 99.2 | 3.9 |
| 2. | Brun, *et al.* | TA | 10741 | 8–38 | 99.9 | 1.7 |
| 3. | Jackson and Wapner | TA | 11600 | 9–12 | 99.7 | 1.9 |
| 4. | Williams, *et al.* | TC | 2949 | 9–12 | 99.7 | 1.9 |
| 5. | Brambati, *et al.* | TC/TA | 10000 | 8–32 | 99.7 | 2.6 |
| 6. | Gogate, *et al.* | TC/TA | 10050 | 9–28 | 98.8 | 2.1 |

(References 12–17)

*in situ to a appropriately equipped and staffed facility rather than transferring a critically ill foetus after delivery*. The couple as well as the family should be properly counseled about the natural history of the disorder, special facilities like special diet/medication needed and the nature of post-delivery management.

In case of sad outcomes like termination of an affected pregnancy, stillbirths/ neonatal death it is utmost important for the treating physicians to put across the need for confirmatory tests like postmortem, genetic/metabolic tests in a sympathetic but firm manner, this should be done before the process of delivery/MTP is initiated. The couple and the family are in a state of grief and shock and are unable to grasp the importance of such studies from future pre-conception counseling and evaluation. Properly conducted studies like these can be very valuable for confirmation of antenatal diagnosis, risk assessment, preconception evaluation and appropriate tests to be done in future pregnancies (*refer to* Chapter 25: Role of perinatal pathologist in preventive genetics). Virtual postmortem evaluation by non-invasive imaging modalities like MRI, skeletal X-ray study can be used in cases where the request for postmortem is refused, to get better idea about the details of structural anomalies diagnosed antenataly.

### *Presymptomatic and predictive genetic diagnosis*

After the advancements in laboratory technologies, better understanding of the structure and functioning of human genome achieved by the completion of human genome project, we are able to diagnose or do screening of asymptomatic carriers in a large number of medical disorders at molecular level. With the availability of targeted Micro-Array panels for specific dosorders, EXHOME studies, NGS it is possible to pick-up the disorder at an overt stage, so that early preemptive treatment can be started so as to increase chances of survival and preserve quality of life. Identification of carriers in other family members can enable required surveillance tests which will permit timely diagnosis and appropriate therapy. Several familial cancers (familial adenomatous polyposis, breast cancers, retinoblastoma, von Hippel-Lindau disease, etc.), adult polycystic kidney disease and Huntington's disease are some of such disorders.[34]

Of course such testing has its own ethical dilemmas like confidentiality of the client versus right of relatives to know the lab results, misuse of such information by third parties like insurers, employees governments with discrimination against the individual and prolonged period of anxiety when there is no clinical disease as yet (*refer to* Chapter 27 on ethical and medicolegal problems for more details).

## CONCLUSIONS

The twenty second century will be dominated by genetics, bio-informatics, its second decade is already getting over! With vast knowledge generated, by the recently completed Human Genome Project, about the structure and function of human genome in health and disease we are on the threshold of a revolution in field of screening, diagnosis and management of a large number of genetic anomalies. As most of the genetic disorders/ birth anomalies are not curable once they are manifested fully, only preventive genetics initiative will be more effective in alleviation of the significant pregnancy wastage, morbidity and mortality due to such genetic disorders. .

It will take a shift in the mind set of general population and medical and paramedical workers and a concerted, multispecialty approach spanning all streams and branches of medicine and other related faculties that will yield the desired results. The spectacular advances in the fields of biotechnology, genetic engineering and pharmacogenetics are double edged weapons and should be handled in a responsible and far sighted manner to avoid problems of eugenics, discrimination, ethical and religious insensitivity. The clash of maternal and fetal interests will also

Chapter

2

# Burden of Genetic Disorders in India

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## INTRODUCTION

India has a population of more than a billion people, with almost 25 millions annual births. Combine this with high rates of consanguinity in many communities, endogamous marriages in various ethnic groups, poor nutritional status (low folate levels) of the mothers and high incidence of infections, and the stage is set for a high frequency of genetic disorders and birth defects. We review the burden of genetic and genetically related disorders that are relevant for preventive intervention.

Genetic diseases occur in two waves—one at birth and one later on in adult life. In the current paper we discuss the disorders that occur in early life, and do not discuss the disorders in adult life like coronary artery disease, hypertension, diabetes mellitus, and mental illness, although they have a significant genetic component.

Table 2.1 summarizes the frequency of genetic disorders/related disorders observed at birth in India. These data are collated from various published sources.[1, 2]

## CONGENITAL MALFORMATIONS

It is intriguing that the malformation rate varies little in different parts of the world. It is possible that Homo sapiens can only tolerate a certain load of malformations, say around 2–4%. In India, a meta-analysis of almost all published studies on congenital malformations showed the frequency to be 19.4 per 1000 on analysis of 301,987 births[3]. A more recent study[4] carried out in three centers (Bombay, Delhi and Baroda) on 94,610 newborns by using a uniform proforma showed a frequency of 2.03%. Expectedly, the malformation rate among stillbirths is much higher (13.6%).

**Table 2.1:** Burden of genetic diseases at birth in India

| *Disorder* | *Incidence* | *Number per year* |
|---|---|---|
| Congenital malformations | 1 in 50 | 595,096 |
| G-6-PD deficiency | 1 in 10–30 (M) | 390,000 |
| Down syndrome | 1: 1139 | 21,412 |
| Congenital hypothyroidism | 1: 2500 | 10,400 |
| Beta-thalassemia | 1: 2700 | 9,000 |
| Sickle cell disease | | 5,200 |
| Amino acid disorders | 1:2347 | 9,760 |
| Other metabolic disorders | 1:2500 | 9,000 |
| Duchenne muscular dystrophy | 1:5000 (M) | 2,250 |
| Spinal muscular atrophy | 1:10,000 | 2,250 |

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