Structural chromosomal abnormalities in children with Intellectual disability and parental balanced chromosomal rearrangements: Importance of genetic counselling.

Santhi S[1], Sherrin T Alex[1], Aswathy C.G [1], Babu George [1], Sankar V H[1*]

[1] Genetic Clinic, Department of Pediatrics, SAT Hospital, Government Medical College,*
[1]Genetic Lab, Child Development Centre, TVPM.

Introduction: Intellectual disability/Mental retardation (MR) is a variable, heterogeneous manifestation of central nervous system dysfunctions, occurring in 1-3% of general population. Developmental Delay/Mental retardation (DD/MR) can be categorized as syndromic, or nonsyndromic; and could or could not be associated with dysmorphic features and multiple malformations. Causes of DD/MR are numerous and include genetic and environmental factors. Genetically determined MR aetiology (comprising chromosomal aberrations, single-gene disorders, and other genetic conditions) account by itself for 17 to 41% of cases; however chromosomal abnormalities have been documented as a single most common cause. The frequency of chromosome anomalies [numerical and structural] detected by karyotyping in patients with DD/MR was variable and estimated between 9% and 36%. It also accounts for 30-40% of severe mental retardation, and 10% of mild mental retardation. Trisomy 21 remains the commonest single cause of mental retardation with its incidence 1:650 -1:1000 live births.

The accurate diagnosis of the chromosomal abnormality is required for proper Genetic Counselling and Prenatal diagnosis. In many cases the abnormalities are inherited from one of the parent where the parent is phenotypically normal, but having balanced chromosomal rearrangements. So parental karyotypes will help to delineate the structural abnormality in the proband. Here we summarize the result of the cytogenetic study performed on 855 mentally retarded children consecutively referred to the Genetics Lab of Child Development Centre, Trivandrum.

AIM: The aim of the study was to describe the importance of Cytogenetics in identifying the chromosomal aberrations in children having mental retardation other than Down Syndrome and its role in prenatal diagnosis.

Study Subjects: The study is a retrospective data analysis done at the Genetic Lab of Child Development Centre, Government Medical College, Trivandrum. A total of 3180 cases were referred for Karyotyping during Nov 2013 to Nov 2021, (8years) with various clinical indications, of which cases with mental retardation (MR)/global developmental delay (DD), multiple malformation (MM) accounts for 855 cases [excluding Down syndrome].

Methodology: Cytogenetic analysis was performed on the peripheral blood sample by Phytohemaglutinin stimulated lymphocyte microculture method followed by GTG-banding method to study the structural variations. For cytogenetic analysis 2 ml heparinized blood samples were collected cultured for 72hrs, harvested and the slides for metaphase study were prepared; the slides were stained using Giemsa stain. Metaphases were studied under oil immersion objective, captured and karyotyped using the ASI [Applied Spectral Imaging] software [USA]. For each sample, 20 metaphases were screened and were karyotyped. All

chromosomal abnormalities were recorded according to the International System for Human Cytogenetics Nomenclature 2020.

Results: Among the 855 MR screened subjects [MR/DD n=242; MR/DD/Dysmorphism n=480, MR/DD/MM n=133], 448 were males and 407 were females. Chromosomal Abnormalities were identified in 75 cases (8.7%) altogether, with 4.5% in MR/DD, 8% in MR/DD/Dysmorphism and the highest in MR/DD/MM with 18.7%. The abnormalities include aneuploidies (n=20, 2.3%) and structural abnormalities (n= 55, 6.4%). In the present study we are focussing mainly on the structural abnormalities. The structural abnormalities obtained in these groups include translocation, deletion, duplication, addition/derivative chromosome, ring chromosome etc .

As the next step to delineate the structural abnormality in children with MR/DD/Dysmorphism/MM [n=55/855, 6.4%], parental karyotype has been performed in 48 cases. Out of which, 20 cases revealed one of the parents as a balanced translocation carrier [42%1. All the couple having carrier status were counselled regarding the risk of miscarriage or having a baby with a serious chromosomal abnormality in next pregnancy. They were also counselled regarding the importance of prenatal diagnosis in future pregnancies.

Conclusion: In conclusion, this study illustrate the contribution of cytogenetics in detecting the abnormalities that lead to the pathogenesis of MR. Therefore cytogenetic analysis is recommended for every individual with idiopathic MR. This can help the management of the MR patient much better. In addition, by discovering the cause of MR, e.g., deletion or duplication/trisomy of a chromosomal segment resulting from a paternal/maternal balanced translocation, prenatal diagnosis could be applied for future pregnancies, thus preventing the birth of another MR infant(s). Advanced molecular cytogenetic technique like microarray helps in the delineation of chromosomal anomaly in MR children. But this is not helpful for an effective genetic counselling for the parents regarding next pregnancy. So Cytogenetic analysis being less costly than the higher end techniques, parental karyotype should be considered as the initial investigation for all the children harbouring a structural abnormality for the proper management, genetic counselling and prenatal diagnosis.