To determine the frequency of subtelomeric abnormalities in children with idiopathic mental retardation

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ABSTRACT

BACKGROUND

Cross-sectional study was carried out to determine the frequency of subtelomeric abnormalities in children with idiopathic mental retardation (MR).

METHOD

Multiplex ligation-dependant probe amplification technique was used to detect subtelomeric abnormalities.

RESULTS

Out of 35 children, 21 (60%) were males. Family history of MR was present in 23%. Main clinical features included speech delay in all motor delay cases (83%) and non-specific dysmorphic features (77%).

CONCLUSION

Associated clinical features were more in children with intelligence quotient (IQ) < 50 ($P < 0.05$). Subtelomeric deletion (4q35) was observed in one child.

MJAFI 2011;67:326–328

Key Words: dysmorphic features; idiopathic mental retardation

INTRODUCTION

Mental retardation (MR) is defined as “significantly sub-average intelligence quotient (IQ)” (≤ 70 , 2 SD below mean on WISC [the Wechsler intelligence scale for children]).¹ Diagnosis is not possible until the child is older than 5 years of age, when standardised measures of intelligence become reliable and valid. Aetiology of moderate to severe MR can be determined in 60–70%, with 40% of them being due to chromosomal anomalies.² Micro deletions and subtle rearrangements that disrupt genes in the telomeric region can cause MR.³ Subtelomeric region

is just proximal to the telomere composed of highly polymorphic repetitive DNA sequences that are typically situated adjacent to gene rich areas. There are conflicting reports and wide variations ranging from 0.5% to 35% in the frequency of subtelomeric rearrangements and deletions in children with idiopathic MR.⁴ Present study was conducted to find its frequency in such children in a service tertiary care centre.

MATERIALS AND METHOD

This was a cross-sectional study done over a two-year period. The study population constituted 35 children of either sex with idiopathic MR attending paediatric outpatient department (OPD) at a tertiary care centre. Children aged 5–14 years of either sex, diagnosed as idiopathic MR were included in the study. Children < 5 years of age, children with specific dysmorphic features like Down's syndrome, children with known causes of MR like history of perinatal insult, neuro-metabolic and neuro-degenerative disorders, infections like subacute sclerosing panencephalitis (SSPE), etc. were excluded from the study.

Detailed history included antenatal, perinatal, postnatal and family history to rule out any possible cause responsible for MR. Detailed examination was carried out in each child to look for dysmorphic features, neuro-cutaneous markers, anthropometry, organomegaly, neurological deficits, and malformations. Hearing assessment, ophthalmic examination, and IQ assessment was done in all the children.

Investigations included magnetic resonance imaging (MRI) brain, electroencephalography (EEG), Thyroid function tests and urine for amino acids in all the children. Screening for neuro-metabolic, neurodegenerative disorders or chronic central nervous system (CNS) infections like SSPE was individualised and children found to be positive were excluded. Karyotyping using G banding technique⁵ and multiplex ligation-dependant probe amplification (MLPA) technique, a variation of polymerase chain reaction⁶ was used to detect subtelomeric abnormalities (Department of Genetics, Sir Ganga Ram Hospital, New Delhi).

RESULTS

Clinical Features

Among the study group 35 children, 21 (60%) were males with a vast majority (42%) being in the age group of 6–8 years. Mean age was 9 ± 2.466 years.

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Received: 31.05.2010; Accepted: 29.07.2011
doi: 10.1016/S0377-1237(11)60077-4

Family history of MR was present in 23% and that of consanguinity in 9%. Speech delay was observed in all and motor delay in 83%. Sleep disturbances in the form of either sleeping less, difficulty in initiation of sleep or fragmented sleep in 63%. Non-specific dysmorphic features like hypertelorism, slanting eyes, large/small ears, thick nose, and frontal prominence was observed in 77%. Prominent behaviour problems observed were attention deficit/hyperactivity disorder (ADHD) (76%) and autistic spectrum of behaviours (46%). Short stature and failure to thrive was seen in 20% and 40%, respectively. Microcephaly was observed in 40%. Electroencephalography abnormalities in the form of slowing, sharp waves, and spikes sharp waves were seen in 20%. Intelligence quotient <50 was seen in 80% of the cases.

Clinical Features in Relation to Dysmorphism

Predominant clinical features among this group included speech delay (100%), motor delay (89%), ADHD (74%), autistic features (41%), disturbed sleep (41%), and failure to thrive (44.4%). Among children who were not having dysmorphic features, main clinical features were speech delay (100%), motor delay (63%), ADHD (75%), and autistic behaviour in 62.5%.

Clinical Features in Relation to Intelligence Quotient

In the group of children with IQ <50 (moderate to severe MR), majority of children were females (71%). The main clinical features in this group were speech delay (100%), motor delay (82%), dysmorphic features (82%), ADHD (75%), autistic symptoms (46%), and microcephaly (43%). Among children who were having IQ >50 (mild MR), majority were males (86%). The predominant clinical features in this group were speech delay (100%), motor delay (86%), dysmorphic features (57%), ADHD (71%), autistic symptoms (43%), and EEG abnormalities (29%).

The presence of clinical symptoms were more in children with IQ <50 with the mean of six clinical features as compared to children with IQ >50 with a mean of four features (approximately).

Subtelomeric Deletion

Mentally subnormal children having normal karyotyping were considered for this study. Subtelomeric deletion (4q35) was observed in one child (2.85%). He was a male child born to non-consanguineous parents, there was no history of MR in the family, he was having speech and motor delay, dysmorphic features, ADHD, and failure to thrive.

DISCUSSION

Mental subnormality occurs in 6–20 cases per 1,000 of general population. Occurrence is more common in boys with the boys to girls ratio ranging between 1.3:1 and 1.9:1.⁷ In the present study also, the male to female ratio is 3:2. Maximum children (42%) are in the age group of 6–8 years. This is because valid IQ assessment is possible only after age of five years and this is the age when they entered school, where they are subjected to IQ assessment, if not able to perform well.

In the present study, 23% cases have family history of MR. Common familial causes of MR are hypothyroidism, fragile X syndrome, and chromosomal disorders⁸ with 80% having severe disability. This is comparable with the available literature.⁹ Common clinical features in children with MR are dysmorphic features, failure to thrive, global developmental delay, and multiple congenital malformations. In this study speech delay is observed in all and dysmorphic features in 77%. Multiple congenital deformities are not seen in any case probably because of early demise of such children.

Such children are difficult, destructive, and antisocial. Temper tantrums, emotional and learning disabilities, autistic spectrum disorders, and ADHD are common features.¹⁰ Prominent behaviours observed in the present study are ADHD (76%) and autism.

Dysmorphological examination and syndromic recognition is critical for the diagnosis of MR and this examination is contributory to the diagnosis in 79% and essential in 62%.¹ The number of surface anomalies is directly related to the increased chances of brain abnormalities. If there are three dysmorphic features chances of mental or developmental delay is 42%.¹

Subtelomeric deletion (4q35) is observed in one child. Children with non-specific dysmorphic features have more chance of subtelomeric re-arrangements. Gopalrao et al² in accordance with the other authors found subtelomeric deletions in about 28% children with non-specific dysmorphic features.¹¹

Deletion 4q syndrome, a de novo (spontaneous) deletion is a rare genetic error. This error occurs very early during embryonic development that occurs for unknown reasons sporadically. Distinct phenotype depends on the size of deletion. 4q31 has been proposed as the minimal critical region most likely responsible for the 4q syndrome. Deletion of 4q32 is similar to 4q31. More distal deletions at 4q33, 4q34 and 4q35 are associated with a less severe clinical phenotype. Estimated prevalence of 4q35 deletion is around 1 in 20,000. This deletion is associated with facio-scapulo humeral muscular dystrophy (FSHD) in the late age.¹²

To conclude, sub-telomeric rearrangements are low in frequency (2.8%). This is in accordance with other published studies with strict selection criteria. The wide variation in the incidence is because of selection criteria used in different studies and diverse prevalence. The best approach to diagnose idiopathic MR is high resolution chromosomal analysis followed by targeted fluorescent in situ hybridisation (FISH) studies. Subtelomeric FISH studies might still be warranted and useful in those cases where there is family history of idiopathic MR. It is recommended that large studies with strict selection criteria may be carried out in children with idiopathic MR when high resolution chromosomal analysis and targeted FISH studies are not contributory. Routine such testing in children with MR is not recommended.

ACKNOWLEDGEMENT

The authors acknowledge Dr IC Verma, Head of the Department and Dr Ratna Puri, Consultant Genetics, Department of

Genetics, Sir Ganga Ram Hospital, New Delhi for carrying out the genetic evaluations in these children.

Intellectual Contributions of Authors

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Drafting and manuscript revision: Brig KS Rana

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CONFLICTS OF INTEREST

This study has been financed by the research grants from the office of the DGAFMS.

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