Original article

Cytogenetic Findings in Patients With Intellectual Disability/Mental Retardation and Dysmorphic Features in Eastern Croatia

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Abstract

Introduction: Numerical and structural chromosomal aberrations are some of the most common causes of intellectual disability/mental retardation (ID/MR), especially syndromic, and they represent about 10% of ID/MR that can be detected using cytogenetic methods.

Aim: The aim of this study is to show the results of cytogenetic findings in 340 patients with ID/MR and dysmorphia and/or multiple malformations in Eastern Croatia, examined at the Paediatric Clinic of the Clinical Hospital Centre Osijek and the Medical Genetics Laboratory at the Faculty of Medicine Osijek.

Methods: Cytogenetic analysis of 340 samples from patients with ID/MR and/or dysmorphia was conducted using G-banding with Trypsin/Giemsa (GTG) and fluorescent in situ hybridization (FISH).

Results: A total of 340 patients with ID/MR with dysmorphia and/or multiple malformations were referred for cytogenetic evaluation. The age range of patients was 0-18 years. The analysis included 221 boys (65%) and 119 girls (35%). A chromosomal aberration was found in 24.5% of patients. Numerical aberrations (aneuploidy) were seen in 64 patients (18.8%). The most common type of autosomal aneuploidy was trisomy 21, found in 14.7% of patients. Sex chromosome aneuploidy was detected in 2.6% of patients. Structural abnormalities were found in 6.5% of patients.

Conclusion: The results of our study show that cytogenetic analysis in patients with ID/MR should nowadays be applied when aneuploidies are suspected, since the first-line genetic test for patients with ID/MR, especially non-syndromic, is the Array Comparative Genomic Hybridization (aCGH).

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Introduction

Intellectual disability/mental retardation (ID/MR) is defined as disability characterized by significant limitations in intellectual functioning and adaptive behaviour, covering everyday social and practical skills and starting before the age of 18 (1). It can be syndromic and non-syndromic. The worldwide prevalence of ID/MR is about 2.3% (2). Genetic causes of ID/MR are considered to account for 25-50% of cases (3). Numerical and structural chromosomal anomalies are some of the most common causes of ID/MR, especially syndromic, and they represent about 10% of ID/MR that can be detected with conventional cytogenetic methods (4). Major autosomal and sex chromosome aberrations often cause a number of phenotypic features, such as cardiac anomalies, infertility and growth deficiency (5). In medical genetics, cytogenetic analysis is an important source for evaluation of specific birth defects, genetic disorders, developmental delay and ID/MR (6).

Around 1,000 chromosomal disorders have been reported (7). ID/MR is one of the reasons for the referral of patients and families to genetic counselling. Identification of the causes of syndromic and non-syndromic ID/MR in a patient is very important because of the consequences it has for the prognosis, risk of occurrence in other family members, and prenatal diagnosis. Here we will summarize the result of a cytogenetic study performed on 340 patients with ID/MR and dysmorphia and/or multiple malformations in Eastern Croatia, who were referred to the Paediatric Clinic of the Clinical Hospital Centre Osijek and the Medical Genetics Laboratory at the Faculty of Medicine Osijek.

Materials and Methods

In this retrospective study we included 340 patients (221 boys and 119 girls) examined in the Paediatric Clinic of the Clinical Hospital Centre Osijek and the Medical Genetics Laboratory at the Faculty of Medicine Osijek, who have the diagnosis of ID/MR with dysmorphic features and/or multiple malformations. The evaluation included physical examination and collection of family medical history. The physical examination was focused on dysmorphological and neurological evaluation, congenital malformations, somatometric measurements and behavioural evaluations. In patients with neurological symptoms, such as epilepsy and macro- or microcephaly, neuroimaging was performed for evaluation of brain malformations. A written informed consent document was signed by the child's parent/guardian for cytogenetic testing.

Cytogenetic methods

Peripheral venous blood was collected by qualified medical staff and sent to the Medical Genetics Laboratory of the Faculty of Medicine Osijek. Blood was sampled once by venepuncture and collected into tubes with anticoagulant Na-heparin. Once received, the samples in the laboratory were identified by a unique laboratory number. Cultivation of peripheral blood cells for the purpose of karyotyping was done using a modified Moorhead method from 1960 (8). The chromosomes were analysed using a light and fluorescence microscope (Olympus BX61) and a digital camera (Diagnostic Instruments 0.7x HR070-CMT) coupled with the appropriate software (Cytovision, Applied Imaging), in accordance with European guidelines for constitutional cytogenomic analysis, European Journal of Human Genetics (2019) 27:1–16. For the purpose of the FISH analysis, in accordance with the suspected structural chromosomal anomalies, we used different locus-specific probes, whole-chromosome paint probes, arm-specific probes, centromere probes and subtelomere probes.

Results

A total of 340 patients with ID/MR with dysmorphic features and/or multiple malformations were referred for cytogenic evaluation. The age range of the patients was 0-18 years. We analysed 221 boys (65%) and 119 girls (35%). Out of 340 patients, chromosomal abnormalities were found in 76 patients (24.5%).

Numerical chromosomal aberrations (aneuploidy) were detected in 64 patients (18.8%). The most common type of autosomal aneuploidy was trisomy 21, which was found in 50 patients (14.7%). Sex chromosome aneuploidy was detected in 9 patients (2.6%). The results are listed in Table 1.

Table 1. Numerical chromosome aberrations (N = number)

Syndrome	Karyotype	N
Down syndrome, common type	47,XX,+21	24
	47,XY,+21	24
Down syndrome, translocation type	46,XY,+21,rob(14;21)(q10;q10)dn	1
Down syndrome, mosaicism and translocation type	mos 47,XX,+21,der(21;21)(q10;q10)der(21;21)(p10;p10)[71]/46,XX,der(21;21)(q10;q10)der(21;21)(p21;21)(p10;p10)[29]dn	1
Edwards syndrome	47,XX,+18	2
Patau syndrome	47,XX,+13	2
Klinefelter syndrome	47,XXY	5
Turner syndrome	45,X	2
Triple X syndrome	47,XXX	2
Klinefelter syndrome/Down syndrome	48,XXY,+21	1

Structural chromosomal aberrations were detected in 22 patients (6.5%). Patients' karyotypes and phenotypes are listed in Tables 2.a. and 2.b.

Table 2.a. Structural chromosome aberrations in patients with ID/MR (M – male; F – female)

Patient	Sex	Phenotype	Karyotype
1	F	Large neurocranium, low posterior hairline, broad nasal bridge, low-set ears, synophrys, strabismus, hypertelorism, epicanthal folds, micrognathia, irregular teeth growth, short fingers with clinodactyly. Hyperactivity	46,XX,der(2),t(2;4)(p25.1;q31.3)pat
2	M	Exophthalmos, epicanthal folds, wide nasal bridge, high-arched palate, irregular teeth growth, low posterior hairline, low-set ears, long fingers and wide thumbs	46,XY,der(1)t(10;11;1)(10pter→10p11.2::11q25→11q23::1p34.3→1qter)mat ,der(11)t(1;11)(p34.3;q23)mat,t(18;19)(q23;p13.3)dn
3	F	Microcephaly, short stature, brachycephalic head, microphthalmia, high-arched palate, hypotonia, epilepsy	47,XX,+der(22),t(X;22)(q28;q11.2)mat
4	M	Microcephaly, antimongoloid slant of eyes, microphthalmia, narrow palpebral fissures, bulbous tip of nose, small mouth and cheilognathopalatoschisis, low-set ears, micropenis, hypospadias, small hands, camptodactyly of the third and fourth finger on both hands, syndactyly of the third and fourth toe and hypoplastic second toe on the right foot. Ductus arteriosus	46,XY,del(2)(q31q33)
5	M	Flat occiput, hypertelorism. Tracheoesophageal fistula	46,XY,r(22)dn
6	M	Sharp hair, low posterior hairline, wide nasal bridge, low-set ears, clinodactyly, hirsutism. Atrial septal defect and cryptorchidism	46,XY,der(8)t(4;8)(4pter→4p16.1::8p23.1→8qter)dn

Table 2.b. Microdeletion syndromes (N = number; P = percentage)

Syndrome	Karyotype	FISH	N	P
DiGeorge syndrome	46,XX	46,XX.ish del(22)(q11.2q11.2)(HIRA-)	1	1.1%
	46,XY	46,XY.ish del(22)(q11.2q11.2)(HIRA-)	3	
Prader-Willi syndrome	46,XX	46,XX.ish del(15)(q11.2q11.2)(SNRPN-)	2	
	46,XY	46,XY.ish del(15)(q11.2q11.2)(SNRPN-)	2	1.5%
Prader-Willi syndrome – uniparental disomy (UPD)	46,XY	/	1	
Williams-Beuren syndrome	46,XX	46,XX.ish del (7)(q11.23q11.23)(ELN-)	1	
	46,XY	46,XY.ish del (7)(q11.23q11.23)(ELN-)	1	0.5%
Cri du Chat syndrome	46,XY,del(5)(p15.1)dn	46,XY,del(5)(p15.1).ish del(5)(p15.2)(D5S23-,D5S721-)dn	1	
	46,XY,del(5)(p14.2)dn	46,XY,del(5)(p14.2).ish del(5)(p15.2)(D5S23-,D5S721-)	1	0.5%
Wolf-Hirschhorn syndrome	46,XY,del(4)(p15.3)dn	46,XY,del(4)(p15.3).ish del(4)(p16.3)(WHSCR-)dn	1	
	46,XX,del(4)(p15.32)dn	46,XX,del(4)(p15.32).ish del(4)(p16.3p16.3)(D4S96-, D4Z1+, D4S3360-)	1	0.5%

Patient 1's karyotype is 46,XX,der(2),t(2;4)(p25.1;q31.3)pat. The FISH method (probes Tel2p, CEP2, WHSC1, Tel4q) shows partial monosomy 2p and partial trisomy 4q. The father's karyotype is 46,XY,t(2;4)(p25.1;q31.3). The FISH method (probes Tel2p, CEP2, WHSC1, Tel4q) shows that the father has a balanced reciprocal translocation between chromosomes 2 and 4. The mother has a normal karyotype.

Patient 2's karyotype is 46,XY,der(1)t(10;11;1)(10pter→10p11.2::11q25→11q23::1p34.3→1qter)mat,der(11)t(1;11)(p34.3;q23)mat,t(18;19)(q23;p13.3)dn. The FISH method (probes for centromere – 11, 18, subtelomere – 11qter, 18qter, 19pter, wcp – 1, 10, 11) shows an unbalanced complex chromosomal rearrangement that involves chromosomes 1, 10, 11, 18 and 19. Derivative chromosome 1 in the patient is inherited from the mother. Reciprocal translocation 18;19 is of de novo origin. This is an unbalanced karyotype with 11q25→qter deletion and 10pter→10p11.2 dupllication. The mother's karyotype is 46,XX,der(1)t(10;11;1)(10pter→10p11.2::11q25→11q23::1p34.3→1qter),der(10)t(10;11)(p11.2;q25),der(11)t(1;11)(p34.3;q23),t(13;18)(q14;p11.32)dn. The FISH method (probes for centromere – 1, 10, 11, 18, subtelomere – 10pter, 11qter, 18pter, 18qter, MCB for chromosome 1, 10, 11, 13, 18, 19, ASP – 1p, 11q, 13q, 10p, wcp - 13) shows a balanced complex chromosomal rearrangement that involves chromosomes 1, 10, 11, 13 and 18. The karyotypes of the mother's parents are normal.

The sister's karyotype is 46,XX,t(1;11)(p34.3;q23)?mat,t(13;18)(q14;11.32)mat. The FISH method (probes for centromere 10, subtelomere – 10pter, 18pter, 18qter, MCB for chromosome 1 and 11, wcp – 1, 10, 11, 13, 18) shows a balanced complex chromosomal

rearrangement that involves chromosomes 1, 11, 13 and 18, but not chromosome 10. The karyotype shows two reciprocal translocations 1;11 and 13;18. Since derivative chromosome 1 in the mother includes chromosomes 10;11;1, and in the sister only chromosomes 1;11, it is possible that mother has gonadal mosaicism. The mother and sister have normal phenotypes.

Patient 3's karyotype 47,XX,+der(22),t(X;22)(q28;q11.2)mat shows an extra chromosome. The FISH method (probes LSI N25 – 22q11.2, LSI SHANK3 – 22q13.3, CEP X-DXZ1, Xqter - MS607) shows a derivative chromosome that contains a region from chromosome 22 (22pter→22q11.2) and chromosome X (Xq28→Xqter). The mother's karyotype is 46,XX,t(X;22)(q28;q11.2)mat. She has a balanced reciprocal translocation between chromosomes X and 22, which she inherited from her mother, whose karyotype is 46,XX,t(X;22)(q28;q11.2).

Patient 4's karyotype is 46,XY,del(2)(q31q33). The mother has a normal karyotype, but we do not know the father's karyotype, so we cannot detect the origin of the chromosomal aberration.

Patient 5's karyotype is 46,XY,r(22)dn. The FISH method (chromosome region 22q11.2, 22q12, 22qter) shows deletion of the 22q13 region and de novo formation of ring chromosome 22.

Patient 6's karyotype 46,XY,der(8)t(4;8)(4pter→4p16.1::8p23.1→8qter)dn shows an unbalanced translocation between the short arms of chromosomes 4 and 8. The FISH method (probes WHSC1, CEP4, CEP8) shows segmental trisomy of the chromosomal segment 4pter-p16.1, and deletion of the chromosomal segment 8pter-p23.1. The parents have normal karyotypes.

Discussion

Numerical chromosomal aberrations are common findings that are well-defined clinically, and their prevalence is similar as in the literature. Coco and Penchaszadeh (9) reported on a cytogenetic study conducted on 200 children with ID/MR in Argentina. They found chromosomal aberrations in 21% of patients. Nasiri et al. (10) reported 23.6% of chromosomal aberrations in their study, similar as in ours. Down syndrome is the most common autosomal aneuploidy in our study (14.7%). Our results were consistent with many previous studies (11,12). We found double trisomy in one patient (48,XXY,+21). This is a very rare trisomy with the phenotype of Down syndrome, as features characteristic of the Klinefelter syndrome are not apparent until the post-pubertal stage (13,14,15). There were 0.5% of female patients with the triple X syndrome. This is a very rare syndrome; the phenotype of such women is normal, they are fertile and they have mostly intellectual problems that vary from mild intellectual disabilities, disorders in language development and problems in forming stable interpersonal relationships to severe psychiatric disorders (16). Structural chromosomal aberrations seen in our patients are variable and were found in 6.5% of patients. The study conducted by Celep et al. (17) reported structural chromosomal aberrations in 4.81% of patients with ID/MR and/or multiple congenital malformations. We compared the clinical findings in our patients with similar cases published in the literature.

Patient 1, with partial monosomy 2p and partial trisomy 4q, has facial dysmorphia and moderate ID/MR, but no urogenital and gastrointestinal anomalies or hand anomalies like the patient described in the literature. Clinical phenotypes of 2p;4q are variable because the involved breakpoints vary on a case-by-case basis (18).

In patient 2, 11q25 deletion is related to developmental delay and facial dysmorphia (exophthalmos, epicanthal folds, wide nasal bridge, high-arched palate, irregular teeth growth, low posterior hairline, low-set ears, long fingers and wide thumbs) (19,20). 10p11.2 dupllication is connected with autistic features (21), which are also present. We presume that novel reciprocal translocation 18;19 does not have an impact on our patient's phenotype, since it is related to changes caused by acute lymphoblastic leukaemia (22).

In patient 3, partial monosomy Xq28 could be related to the phenotype listed in Table 2.a.,

since this region contains the MECP2 gene, which causes the Rett syndrome, severe epilepsy and psychomotor delay (23). Partial trisomy 22q11.23, which is distal from the DiGeorge syndrome region of the long arm of chromosome 22, could be responsible for other features: growth delay, hypotonia, severe psychomotor delay (24,25).

The phenotype of patient 4 (microcephaly, antimongoloid slant of the eyes, microphthalmia, narrow palpebral fissures, bulbous tip of nose, small mouth and cheilognathopalatoschisis, low-set ears, micropenis, hypospadias, small hands, camptodactyly of the third and fourth finger on both hands, syndactyly of the third and fourth toe and hypoplastic second toe on the right foot) is similar to the only published case with del(2)(q31q33) (26).

Karyotype 46,XY,r(22)dn in patient 6 is known as the Phelan-McDermid syndrome, which includes hypotonia, developmental delay, dysmorphic features (long narrow head, pointed chin, ptosis, deep-set eyes, abnormalities of toes and nails) (27,28). Our patient has mild dysmorphia, psychomotor delay and tracheoesophageal fistula which has been successfully corrected, but has no abnormalities of toes and nails or other dysmorphic features typical for the syndrome. The clinical picture could be incomplete, so it would be recommended to perform aCGH.

We have compared the similarity of patient 7's features to other patients carrying only a duplication of the distal part of 4p or a deletion of the distal part of 8p or similar, which include low posterior hairline, hirsutism, wide nasal bridge, low-set ears, clinodactyly, atrial septal defect and cryptorchidism (29,30); similar features can be found in our patient.

Other structural aberrations listed in Table 2.b. have a well-defined phenotype (DiGeorge syndrome, Prader-Willi syndrome (PWS), Cri du Chat syndrome, Wolf-Hirschhorn syndrome, Angelman syndrome, Williams-Beuren syndrome). In our study, the most common syndromes are PWS (1.5%) and DiGeorge syndrome (1.1%). DiGeorge syndrome occurs in 1 in 4.000 people (31) and PWS in 1 in 10.000 to 30.000 people (32). It is interesting that we have a very similar percentage of patients with PWS and DiGeorge syndrome, since the prevalence of DiGeorge syndrome is higher than the prevalence of PWS in the general population (31,32). On the other hand, the small percentage of patients with DiGeorge syndrome in our study could be explained by its variable features. The condition may not be identified in people with mild signs and symptoms, or it may be mistaken for other disorders with overlapping features.

Conclusion

The results of our study show the prevalence of chromosomal aberrations in 24.5% of patients with ID/MR and dysmorphia, which confirms similar findings in other screened groups of numerical anomalies. The frequency of aberrations in patients with ID/MR in our study was 18.8%, and the most common aberration was DS, as seen in other studies. Cytogenetic findings of structural aberrations were 6.5%, which is also similar to other studies. The results of our study show that cytogenetic analysis in patients with ID/MR should nowadays be reserved for suspected aneuploidies, since first-line genetic testing for patients with ID/MR and especially non-syndromic patients is aCGH (33,34).

Abbreviations

MR – mental retardation;
ID – intellectual disability;
GTG – G-banding with Trypsin/Giemsa;
CTG – C-banding with Trypsin/Giemsa;
FISH – fluorescent in situ hybridization;
DS – Down syndrome;
PWS – Prader-Willi syndrome;
UPD – uniparental disomy;
aCGH – Array Comparative Genomic Hybridization.

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