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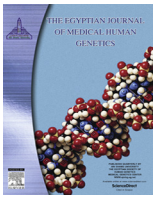

Original article

Yield of karyotyping in children with developmental delay and/or dysmorphic features in Sohag University Hospital, Upper Egypt

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ABSTRACT

Background: Global developmental delay (GDD) represents a measurable lag in a young child's achievement of developmental milestones compared to age matched children. Affection of two or more developmental domains is fundamental for assumption of GDD. Many chromosomal abnormalities are responsible for developmental delay or mental retardation and can be detected using G-banded karyotyping.

Aim of the work: This work aimed to determine the yield of karyotyping in children with GDD and/or dysmorphic features in Sohag University Hospital, Upper Egypt.

Subjects and methods: All children presenting with GDD and/or dysmorphic features, with abnormal karyotyping or other genetic testing were included. Full history, thorough clinical and detailed neurological examinations were done. The results of other investigations done for the patients, including neuroimaging and electroencephalography (EEG), were utilized (if available).

Results: The total number of patients included was 395 patients, out of 646 patients who did karyotype; the mean age of presentation was 24.7 ± 32.1 (SD) months, there were 243 (61.5%) males and 152 (38.5%) females. The positive yield of karyotyping in children with developmental delay and/or dysmorphic features, including classic Down features, was 61.1%; however, with exclusion of Down syndrome and other suspected trisomies, it became 7.4%. The most prevalent chromosomal abnormality was trisomy 21-Down syndrome (364 patients/92.2%), followed by structural chromosomal abnormalities and marker chromosome in 19 patients (4.8%) and, lastly, sex chromosome abnormalities (8 patients/2.0 %). The main complaint was GDD in half of the patients (205/51.9%), while the majority of patients had microcephaly.

Conclusion: G-banded karyotyping is a useful tool with reasonable yield in evaluation of children with developmental delay and/or dysmorphic features, especially in countries with limited resources.

1. Introduction

Global developmental delay (GDD) represents a measurable lag in a young child's achievement of developmental milestones compared to age matched children. Children aged less than six years are considered to have global developmental delay (GDD) if their performance was more than two standard deviations (SDs) below age-matched peers in two or more developmental domains [1–3]. It is considered a common problem, affecting 1–3% of children [4]. The American Academy of Neurology and the Child Neurology Society guidelines regarding evaluation of GDD clarified that several diagnostic tests had a greater than 1% yield. These tests include Giemsa-banded (G-banded) karyotyping, fragile X mental retardation 1(FMR1) gene testing, methyl-CpG binding protein 2(MeCP2) gene testing in girls with moderate to severe impairment, subtelomeric fluorescence in situ hybridization (StFISH) testing, neuroimaging and assessments for visual and hearing deficits. Genetic and metabolic testing were highlighted during the genetic era [5]. There are numerous and heterogeneous conditions causing GDD, with etiological yields ranging from 10 to 80% depending on variations in population characteristics, classification and diagnostic facilities available, such as genetic and imaging technology [6,7]. Retrospective and prospective studies found a yield of around 50% and the conditions were, in order of decreasing frequency; (1) genetic syndromes/chromosomal anomalies, (2) intrapartum asphyxia, (3) cerebral dysgenesis, (4) severe psychosocial deprivation and (5) ante-natal toxin exposure [5–7]. Conventional karyotyping using microscopy techniques or banding can initially detect duplication and recurrent deletions, which lead to many cases of mental retardation (MR). G-banding karyotype analysis

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is a famous technique used to identify individual human chromosomes in many laboratories worldwide and has an estimated yield of at 3% (excluding Down syndrome and other recognizable chromosomal syndromes) [8,9]. G-bands by trypsin using Giemsa (GTG), is performed by chromosome digestion with proteolytic enzymes, followed by Giemsa staining, leading to a characteristic pattern of light and dark bands (G bands) for each chromosome pair detected under a microscope [8]. Although karyotyping has been accepted as the standard for genetic assessment of children with GDD, it lacks the ability to capture chromosomal imbalances smaller than five to 10 Mb [10–12]. Smaller chromosomal gains and losses can be detected by fluorescence in situ hybridization (FISH) and multiplex ligation-dependent probe amplification. However, these techniques can be utilized only for a specific clinical suspicion or for the analysis of subtelomeric regions of the genome known to be frequently affected in developmentally impaired children [13]. There are demanding needs for accurate diagnosis and there is wide use of conventional karyotyping in our locality, in addition to few studies being conducted to address the value and yield of karyotyping in children with global developmental delay and/or dysmorphic features in Upper Egypt.

2. Aim of the work

This work aimed to determine the yield of karyotyping and to explore the pattern of chromosomal abnormalities in children with GDD and/or dysmorphic features in Sohag University Hospital, Upper Egypt.

3. Subjects and methods

3.1. Study design

This study was both prospective and retrospective, observational hospital based study done in the Pediatric Neurology Clinic, Pediatric Department, Sohag University Hospital, Upper Egypt, over a one year period from January 2016 through December 2016. Informed consent of the parents of the children coming for follow up was taken prior to conducting this research and was approved by the Faculty of Medicine, Sohag University Ethics Committee. In addition, it was carried out in accordance with The Code of Ethics of The World Medical Association (Declaration of Helsinki) for experiments in humans.

3.2. Patients

This study included all children who presented to us with global developmental delay, dysmorphic features, hypotonia and or intellectual disability and had abnormal karyotyping in the last eight years. For those children still coming for follow up in our clinic, data was taken from the patients and their parents, whereas for those who missed follow up data was extracted from the patient's files. Exclusion was done for cases that did not have karyotyping; meanwhile, those with normal findings were used only as a reference for positive yield (Fig. 1).

3.3. Methods

The results of karyotyping were reviewed and confirmed. In all cases, routine GTG (Giemsa banding technique) karyotyping was done, in five cases FISH test (fluorescence in situ hybridization) was performed, while in only three cases, studying for fragile-X syndrome was conducted. Karyotyping was requested previously for the patients as part of their diagnostic evaluation.

Patients data were reviewed and clinical history including age, sex, birth order, consanguinity, family history, perinatal, neonatal and developmental history were collected. History of behavioral problems like hyperactivity, aggression and autistic features were also included.

The details of patients examinations took into account general look and the presence of dysmorphic features (slanting eyes,

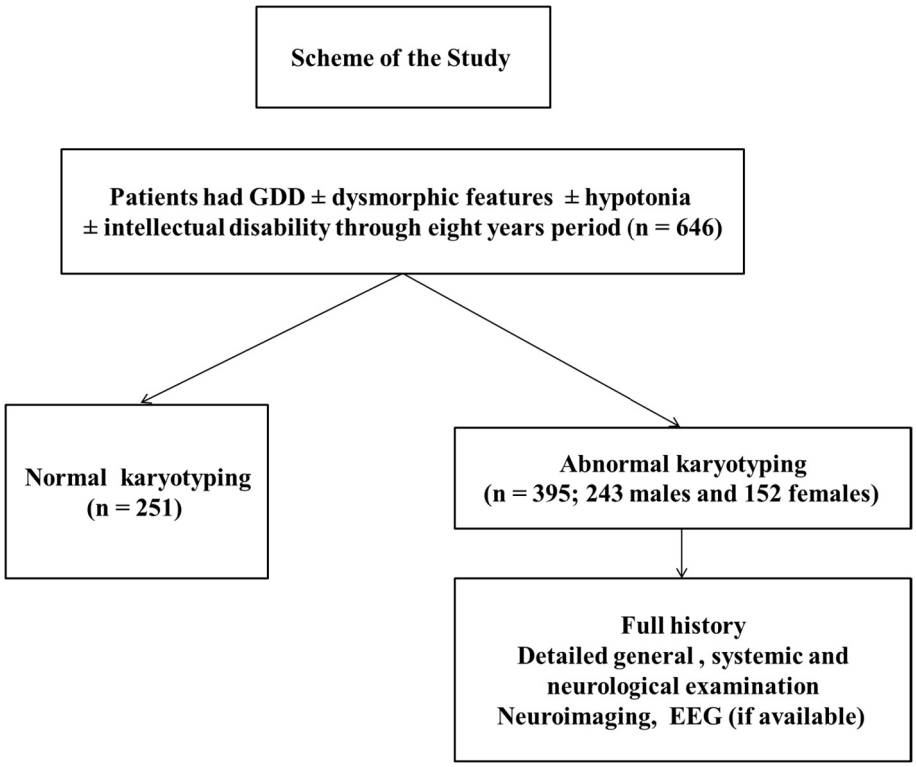

Fig. 1. Scheme of the study.

hypertelorism, depressed nasal bridge, low set ear, brachycephaly), in addition to simian crease, clinodactyly and overlapping of fingers, as well as anthropometric measurements and a systemic and through neurological examination (including muscle tone and stretch reflexes).

Furthermore, the results of other investigations done for the patients, such as computed tomography (CT) and magnetic resonance imaging (MRI) of the brain and electroencephalography (EEG) were included.

3.4. Statistical analysis

The data was subjected to statistical analysis and tabulation using SPSS version 18, then the results were presented to fulfill the objectives of the study.

4. Results

The total number of the patients enrolled in this study with abnormal karyotyping was 395 (61.1%) out of 646 patients subjected to karyotyping. The vast majority of chromosomal abnormalities were trisomy 21-Down syndrome as it was detected in 364 patients (92.2%), and free trisomy 21 (non-disjunction) subtype was the most common as it was found in 356 patients (97.8%), followed by translocations and mosaic trisomy 21 in four patients (1.1%) each. Interestingly, we found one case (0.25%) of mixed abnormality; double aneuploidies involving chromosome 21 and X chromosomes(48 XXY, +21) (Klinefelter/Down syndrome). Other chromosomal trisomies were: Edward syndrome as reported in one case (0.25%) and translocation Patau syndrome was also detected in one case (0.25%) (Table 1) (Fig. 2).

Sex chromosome abnormalities were defined in eight cases (2.0%); of which Turner syndrome was the most common as

Table 1
Distribution of cases according to karyotyping (n = 646).

	No. (%)	Classifications of chromosomal abnormalities, No. (%)	Subtypes of chromosomal abnormalities, No(%)	
Total cases of abnormal karyotype	395 (61.1%)	Trisomy 21 (Down syndrome) 364 (92.2%)	Free trisomy 21 (Non-disjunction Down)	356 (97.8%)
			Translocations	4 (1.1%)
			Mosaicism	4 (1.1%)
		Sex chromosome abnormalities 8 (2%)	Klinefelter syndrome, two cases (47, XXY), and one case (49, XXXXY)	3 (37.5%)
			Turner syndrome, 45, X0	4 (50.0%)
			Extra XX Chromosome, 48, XXXX	1 (12.5%)
		Klinefelter/Down syndrome double aneuploidies of chromosome 21 and X chromosomes[48, XXY, +21]	1 (0.25%)	
		Trisomy 18, Edwards syndrome	1 (0.25%)	
		Trisomy 13, Patau syndrome [46, XX, der(13;14), +13]	1 (0.25%)	
		Structural chromosomal abnormalities and marker chromosome	19 (4.8%)	
		Fragile-X Syndrome [46, XY, Fra (X)(q27.3)]	1 (0.25%)	
Total cases of normal karyotype	251 (38.9%)			

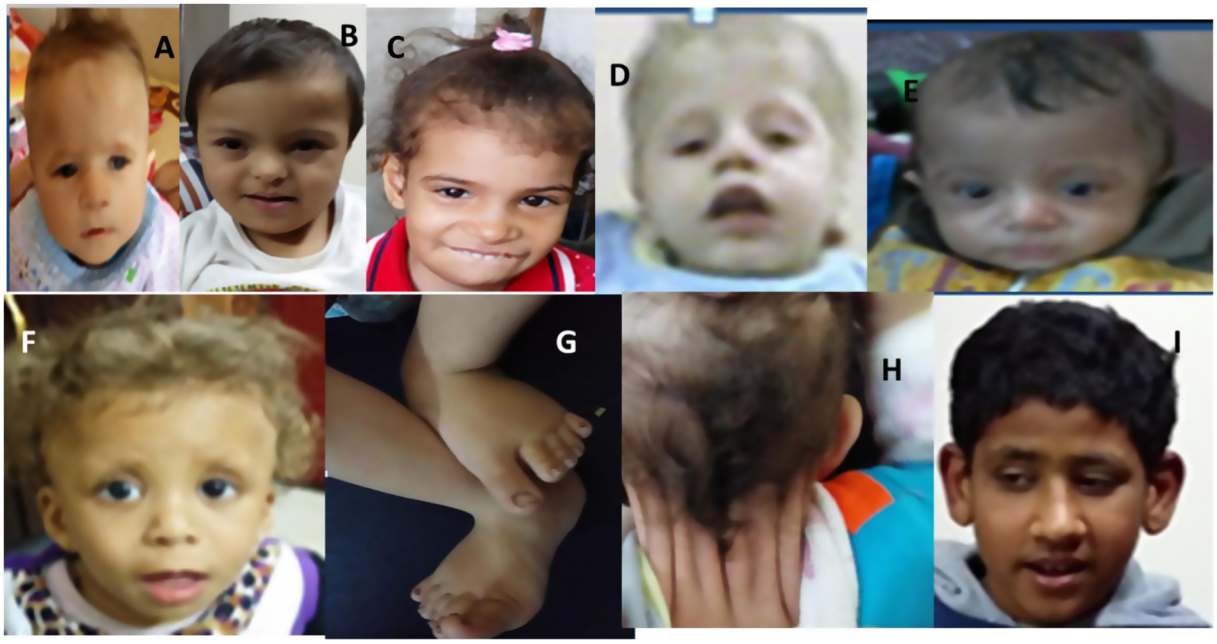

Fig. 2. A: Translocation Patau syndrome[46,XX,der(13;14),+13]. B: Klinefelter/Down syndrome[48, XXY, +21]. C: Extra XX chromosome [48,XXXX]. D, E: Two patients with Klinefelter syndrome[47,XXY]. F: Turner syndrome [45, X0]. G: Foot non pitting oedema in a patient with Turner syndrome. H: Neck webbing in a patient with Turner syndrome. I: Fragile X syndrome [46,XY, Fra(X)(q27.3)].

Table 2
Distribution of structural chromosomal abnormalities and marker chromosome (n = 19).

Chromosome	Chromosomal aberrations	No. (%)
Ch 1	Inversion of chromosome 1[46, XY, inv (1) (p34.2q42)]	1(5.26%)
Ch 3	Deletion at chromosome 3 [46, XX, del(3) (3p25-26)]	1(5.26%)
Ch 4	Deletion of long arm of chromosome 4 [46, XX, del(4)(q25-q27)]	1(5.26%)
Ch 5	Deletion in chromosome 5 [46, XX, del(5)(p 15.2)]	1(5.26%)
	Deletion of short arm of chromosome 5 -5P syndrome [46, XX, del(5)(5p14-5p15.1)]	1(5.26%)
Ch 6	Abnormal chromosome 6 short arm [46, XX, abnormal(6)(p)]	1(5.26%)
Ch 7	Deletion of long arm of chromosome 7 (William Syndrome) [46, XY, del(7)(q)]	1(5.26%)
Ch 7,9	Chromosome 7 and 9 reciprocal translocation[46, XX, t(7,9)]	1(5.26%)
Ch 9	Abnormal chromosome 9, additive material- Piere Rubin Sequence [46, XY, add(9)]	1(5.26%)
Ch 11	Abnormal chromosome 11 (addition material) [46, XY, add(11)(9.25)]	1(5.26%)
Ch 15	Abnormal chromosome 15 with added chromosome material in its short arm [46, XY, add(15)(p)]	1(5.26%)
	Deletion in long arm of chromosome 15 (Prader Willi syndrome) [46, XY, del(15)(q)]	1(5.26%)
Ch 18	Deletion of short arm of chromosome 18[46, XX, del(18)(p11.2)]	1(5.26%)
	Deletion in chromosome 18 [46, XX,del(18)(q22)]	1(5.26%)
Ch 21	Addition at chromosome 21 [46, XY, add(21)(21q22)]	1(5.26%)
Ch 22	Chromosome 22 micro deletion [46, XY, del(22)]	1(5.26%)
Ch Y	Deletion of long arm of Y chromosome [46, XY, del(Y)(q)]	1(5.26%)
Marker Chromosome	Marker chromosome female [47 XX, + marker]	1(5.26%)
	Marker chromosome male [47 XY, + marker]	1(5.26%)

Abbreviations inv: inversion, del: deletion, t: translocation, add: addition, p: short arm, q: long arm.

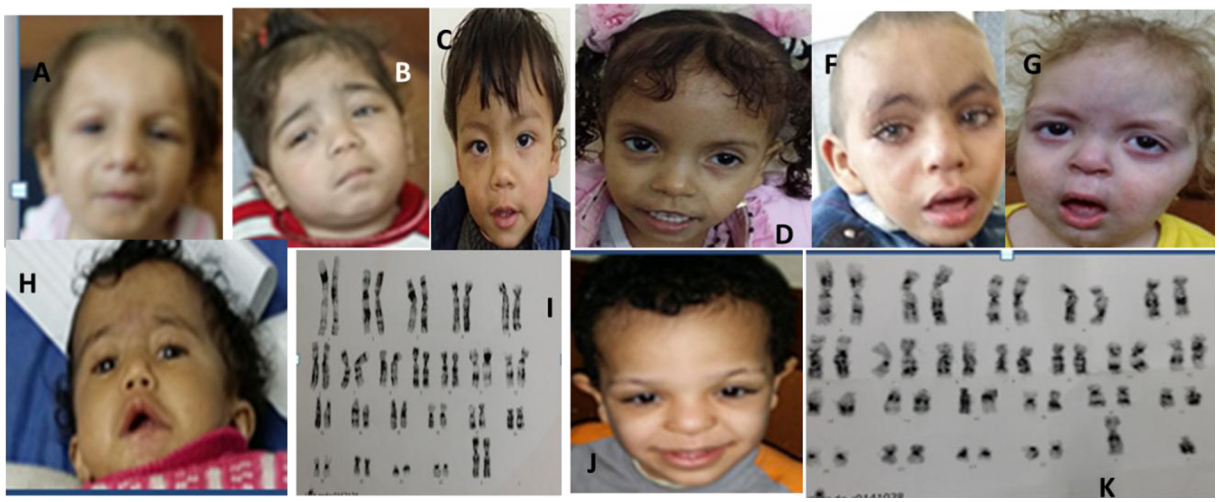

Fig. 3. A: Addition at chromosome 15 [46, XY, Add(15)(p 13)]. B: Deletion in chromosome 18 long arm [46,XX,del(18)(q22)]. C: Inversion of chromosome 1 [46,XY,inv(1)(p34.2q42)]. D: Deletion of short arm of chromosome 18[46, XX, del(18)(p11.2)]. F: Addition at chromosome 11[46, XY, add(11)(9.25)]. G: Reciprocal translocation between chromosome 7 and chromosome 9 [46,XX,t(7,9)(q11.2-p23)]. H,I: Female child with marker chromosome [47,XX, + mar]. J,K: Male child with marker chromosome [47,XY, + mar].

reported in four cases (50.0%), followed by Klinefelter syndrome in three cases (37.5%) and, lastly, an extra X chromosome in one female case (12.5%) (Table 1) (Fig. 2).

Structural chromosomal abnormalities and marker chromosome were detected in 19 cases (4.8%), the most common was chromosome five deletion of short arm, chromosome 15 and chromosome 18 abnormalities, in addition to marker chromosome, were found in two cases (10.5%) each (Table 2) (Fig. 3). Testing for fragile-X syndrome was positive in one case (0.25%) (Table 1) (Fig. 2).

The positive yield of karyotyping in children with developmental delay and dysmorphic features including classic Down features was 61.1%. However, with exclusion of Down syndrome and other suspected trisomies from cases the positive yield was 7.4%.

The mean age of presentation in our study was 24.7 ± 32.1(SD) months, with an age range from one month to 204 months. There were 243 (61.5%) males and 152 (38.5%) females. The most prevalent condition was global developmental delay in half of the patients (205/51.9%), followed by dysmorphic features in 95 patients (24.1%). The 1st child in birth order was the most commonly affected, however other birth orders were reported. Consanguinity was reported in 186 (47.0%) patients, while positive family history of similar conditions or neurological problems was reported in 40 patients (Table 3).

Regarding developmental evaluation: 302 (76.5%) patients had delayed motor development, 385 (97.5%) patients had delayed speech, while 307 (77.7%) patients had delayed social development and, lastly, hyperactivity and autistic features were reported in 33 (8.4%) patients (Table 3).

Neurological evaluation showed that the majority of cases had microcephaly, with a mean head circumference of 41.4 ± 4.7 (SD) cm and a range from 29 cm to 53 cm. Hypotonia was reported in 315 (79.7%) patients while hypertonia was reported in five (1.3%) patients, finally normal tone was found in 75 (19%) patients (Table 4).

Computed tomography (CT) of the brain was done in 41 patients; 16 (39.0%) of them had normal findings, 20 (48.8%) patients had brain atrophy; while three patients had white matter

Table 3
Socio-demographic data and clinical presentation of the studied cases (n = 395).

Variable	Abstract statistic
Age of presentation (months)	
Mean (SD)	24.7 (32.1)
Median (range)	10 (1–204)
Sex	
Male	243 (61.5%)
Female	152 (38.5%)
Complaint	
GDD	205 (51.9%)
DLD and Hyperactivity	78 (19.7%)
Dysmorphic feature	95 (24.1%)
Others(poor feeding, head nodding)	17 (4.3%)
Birth order	
Mean (SD)	3.88 (2.4)
Median (range)	4 (1–15)
Mode	1
Consanguinity	
Yes	186 (47.0%)
No	209 (53.0%)
Positive family history of developmental delay or neurological problems	
Yes	40 (10.1%)
No	355 (89.9%)
Motor development	
Normal	93 (23.5%)
Delayed	302 (76.5%)
Speech development	
Normal	10 (2.5%)
Delayed	385 (97.5%)
Social development	
Normal	55 (13.9%)
Delayed	307 (77.7%)
Hyperactivity and autistic features	33 (8.4%)

Abbreviations SD: standard deviation, GDD: global developmental delay, DLD: delayed language development.

Table 4
Neurological evaluation and investigations done for the studied patients (n = 395).

Variable	Summary statistic
Neurological examination	
Head circumference	
Mean (SD)	41.4 (4.7)
Median (range)	42 (29–53)
Mode	46
Muscle tone	
Normal	75 (19.0%)
Hypotonia	315 (79.7%)
Hypertonia	5 (1.3%)
CT brain	
Normal	16 (39.0%)
Brain atrophy	20 (48.8%)
White matter disease	3 (7.3%)
Corpus callosum agenesis	2 (4.9%)
Not done	354 (89.6%)
MRI brain	
Normal	1 (7.6%)
Brain atrophy	7 (53.8%)
White matter disease	4 (31%)
Corpus callosum agenesis	1 (7.6%)
Not done	382 (96.7%)
EEG finding	
Normal	3 (11.5%)
Epileptic abnormalities	18 (69.3%)
Hypsarrhythmia	5 (19.2%)
Not done	369 (93.4%)

Abbreviations SD: standard deviation, CT: computed tomography, MRI: magnetic resonance imaging, EEG: electroencephalogram.

changes (7.3%). Magnetic resonance imaging (MRI) of the brain was done in 13 patients, brain atrophy was most commonly reported, in seven patients (53.8%). Seizure disorders were found in 10 patients (2.5%), half of them had epileptic spasms (50.0%). Electroencephalography was done on 26 patients; 18 (69.3%) of them had epileptic recording, while a specific hypsarrhythmia pattern was found in five patients (19.2%).

5. Discussion

The need for reliable clinical genetic testing in evaluating patients with developmental delay (DD), mental retardation (MR) and autism spectrum disorders (ASD) with unclear etiology is paramount [14,15].

This study was conducted in a region of limited resources in Upper Egypt, exploring the pattern of chromosomal disorders and yield of conventional karyotyping over the last eight years in children with developmental problems at Sohag University Hospital.

In our study, males were predominant (61.5% vs 38.5%) and this agreed with other studies [7,8]. They found affected males at 74% and 61.2%, respectively. The mean age of presentation of our cases was 24.7 months, while in the study of Srour et al. [7] the mean age was 33.6 months and was 30 months in another study [16].

The positive yield of karyotyping in our series was 61.1% (395 out of 646). This percentage was high compared to other studies. However, with exclusion of Down syndromes and other known trisomies, the positive yield was 7.4%. This was still higher than other studies [9,17], which concluded that the diagnostic yields of conventional cytogenetics and fragile-X syndrome testing in patients with developmental delay/mental retardation (DD/MR) is below 3% and 1.2% respectively. However, the reported yield was about 4%, such as in the studies done by many researchers with a range from (2.9–11.7%) [6,18–24]. On the other hand, higher yields were obtained that could reach 18.6% (6.7–50%), as in other studies [21–23].

Overall, in children with global developmental delay, the causes and risk factors are heterogeneous, so there are marked variations in the yield. Thus etiological yield could reach 50% as reported in two studies [19,25]; they found chromosomal abnormalities in 11.7% and fragile-X syndromes in 3.3%.

In another study of developmental delay, etiological yield was found in 41.6%, chromosomal abnormalities were found in 28% of them, while fragile-X syndromes were found in 6% [19]. Also, other researchers [26] found etiological diagnosis in children with GDD in 63.3% and chromosomal abnormalities were found in 10%. In the study done by Shevell et al. [6], an etiology was found in 61.97% and chromosomal abnormalities accounted for 77% of the cases. Furthermore, in a study done by Srour et al. [7] on patients with global developmental delay, the etiologic yield was also defined as 40% overall and 55% in the absence of autistic features. Focusing on dysmorphic features, they could ascertain an etiologic yield in 52.4% of cases [7]. In another study [16], they found definite etiology for GDD in 54.1% and karyotyping yield was 12.5%, all of them were Down syndrome. In a recent study [8], the yield of karyotyping was 8.4%.

In our study, Down syndrome was detected in 92.2%, sex chromosome abnormalities in 2.0% and structural chromosomal abnormalities in 14.8%. These findings were relatively similar to other researchers [27] working on female mental retardation series who found chromosomal abnormalities in 24%, of which Down syndrome was detected in 83.33% and structural abnormalities in 13.88%, while Turner syndrome was identified in 2.77%. Another study done by Behjati et al. [28] on patients with idiopathic mental retardation from consanguineous marriages, found ten patients (3.10%) showed chromosome abnormalities, the abnormalities

included the following groups: 1) sex chromosomes abnormalities in three patients (0.93%), 2) presence of a high percentage of prometa phase/prophase chromosome spreads, with twisted, curly and poor banding quality and 3) autosomal structural abnormalities.

Furthermore, in a study done by Teixeira et al. [8], the yield of karyotyping in patients with mental retardation was: 67.8% of cases with abnormal karyotyping had structural abnormalities, 29% had numerical abnormalities, sex chromosome abnormalities represented 55.55%, while trisomy 21 was detected in 33.33%.

In this study, we found many structural abnormalities (inversion, deletion, addition and reciprocal translocation, in addition to marker chromosome) affecting many chromosomes (Table 2) and this was comparable to a similar study which identified breakpoints involving many chromosomal regions [8]. Also, another researcher found four patients (1.24%) with unbalanced structural chromosome abnormalities, all of which were unbalanced segregation products of parental balanced rearrangements [28].

Interestingly, we reported two cases of marker chromosome, one male and one female, their main presentation was global developmental delay and dysmorphic features. A comparable study [8], reported three cases with additional marker chromosomes of unknown origin, two of which were mosaic marker chromosomes.

In this work, the most common numerical (also autosomal) chromosomal aberration (aneuploidy) was Down syndrome, as detected in 92.2%. It is considered the most common genetic cause of intellectual disability [29] and moderate mental retardation [17,30].

We identified four patients with Klinefelter syndrome, one of them had double aneuploidies involving chromosome 21 and X c hromosomes(48XXY,+21)(Klinefelter/Down syndrome), two of them had severe mental retardation, marked neurological deficit, intractable seizures and autistic features. The estimated frequency of this disorder is between 1:500 and 1:1000 live births. Patients with Klinefelter syndrome usually have delayed auditory processing, language dysfunction and, in rare cases, severe intellectual retardation [31]. Similarly, we reported four cases with Turner syndrome; those patients, in addition to the unique physical characteristics of this syndrome, have a non-verbal IQ significantly lower than their verbal IQ and commonly require educational intervention for learning disabilities [32,33].

Surprisingly, we reported two cases (brother of a Klinefelter case and sister of an extra X syndrome case) had nearly similar degree of mental retardation and developmental delay, but had normal karyotyping. Comparable results were obtained by Behjati et al. [28].

Epilepsy was reported in 2.5% of the patients; the most common type was epileptic spasms (50%), and the majority of them (four cases/80%) were Down syndrome. This was in accordance with the previous studies concluding that West syndrome constitutes the most frequent of all seizure types in infants with Down syndrome [34–37].

Although our study showed high diagnostic yield for G-banded karyotyping, reaching 61.1% and 7.4% after exclusion of Down syndromes and other known trisomies, there are limitations attributed to the recent assumption that chromosomal microarray (CMA) is increasingly utilized for genetic testing of children with unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD) or multiple congenital anomalies (MCA). And that CMA gives a much higher diagnostic yield (15–20%) for genetic testing of these patients than a G-banded karyotype (~3%, excluding Down syndrome and other recognizable chromosomal syndromes), because of its higher sensitivity for submicroscopic deletions and duplications [9].

6. Conclusions

G-banded karyotyping is a useful tool with reasonable yield in evaluation of children with developmental delay and or dysmorphic features, especially in countries with limited resources. Trisomy 21 (Down syndrome) was the most common chromosomal abnormality encountered in Sohag University Hospital, followed by structural abnormalities and, lastly, sex chromosome abnormalities.

Footnotes

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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