

Phenotypic variance in children with chromosomal aberrations – A cohort study

Alaa Abouzaid¹, Jemila James¹, Emad Shatla²From ¹Registrar, ²Consultant, Department of Pediatrics, King Hamad University Hospital, Busaiteen, Al Muharraq, Kingdom of Bahrain

ABSTRACT

Background: Chromosomal abnormalities are the result of alterations in the number or structure of chromosomes leading to significant human morbidity and mortality. They are responsible for large proportion of miscarriages, developmental delay, disorders of sexual development, congenital malformations, and mental retardation. **Objectives:** The objectives of the study were to find the occurrence of chromosomal abnormalities in infants and children with various phenotypic presentations and to analyze the impact of associated risk factors for chromosomal abnormalities in children. **Materials and Methods:** A retrospective single-center study, based on the outcome data of chromosomal analysis of 112 children admitted to the pediatric department of our hospital over a period of 3 years, was reported. The data were collected from the electronic medical records for analysis, including maternal age, consanguinity, family history of any congenital anomalies and malformations, clinical details, and the results of chromosomal analysis. **Results:** A statistically significant association between the presence of dysmorphic features and chromosomal abnormalities with 3 times increased risk when compared to children with no dysmorphism (relative risk [RR] 3.06, 95% confidence interval [CI] 1.71–5.50, $p=0.0002$). Among the congenital anomalies, the presence of congenital heart defects had strong association and was found to be 43% higher in children with chromosomal abnormalities (RR 1.43, 95% CI 1.10–1.86, $p=0.0069$). Our study demonstrated a strong association for maternal age >35 years and the risk for chromosomal abnormality. It was 1.75 times more than the children born to mothers ≤ 35 years age (RR 1.75, 95% CI 1.29–2.36, $p=0.0003$). **Conclusion:** Cytogenetics has a major role in diagnosis of chromosomal abnormalities, especially in children with dysmorphic features and congenital heart defects. The early diagnosis is important for planning and resource allocation of specialized health services directed toward the families and infants.

Key words: Aberrations, Chromosome abnormalities, Chromosome aberrations, Cytogenetic abnormalities, Cytogenetic aberration


Chromosomal abnormalities occur in approximately 8% of fertilized ova but only 0.6% of liveborn infants. The syndromes caused by chromosomal abnormalities include trisomy 21, trisomy 13, trisomy 18, Turner syndrome, Klinefelter syndrome, as well as chromosomal duplications, deletions, and inversions [1]. Fida *et al.* in 2007 reported that congenital anomalies occur in 3% of all infants worldwide including structural malformation, chromosomal abnormalities, and metabolic disorders [2].

Chromosomal abnormalities can be either inherited from a parent (e.g., translocation) or can develop spontaneously. Hence, chromosomal studies are performed on both the parents and the child with the abnormality. Advances in molecular biology and cytogenetic techniques permit the identification of many diverse types of genomic variants, which contribute to human disease, phenotypic variation, and karyotypic evolution [3].

Nearly 60% of congenital anomalies are of unknown origin. Genetic congenital anomalies, such as chromosomal abnormalities,

have a vast research while those of environmental etiology caused by teratogens, are the least investigated [4]. In addition to genetic causes for congenital anomalies, factors such as infectious agents and environmental agents like radiation lead to chromosomal aberrations [5]. The maternal factors including age, lifestyle, type of pregnancy and maternal health, have also been researched and connected to the occurrence of congenital anomalies [6].

Primary prevention seeks to ensure that the individuals are born free of congenital anomalies. Services for the primary prevention of congenital malformations include basic reproductive health-care approach [7]. Cytogenetic techniques can diagnose chromosomal abnormalities and investigate the possible etiology of birth defects. It is important to know the clinical data of chromosomal abnormalities to explore the corresponding relationship between the observational characteristics of an individual resulting from the interaction of its genotype and the environment [8]. Although congenital anomalies contribute to a significant proportion of perinatal and infant morbidity and mortality, approximately 50% of them are not assigned to a specific cause [9]. However,

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Correspondence to: Jemila James, DNB, Department of Pediatrics, King Hamad University Hospital, Busaiteen, Al Muharraq, Kingdom of Bahrain. E-mail: drjemiben@gmail.com

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consanguineous marriage and maternal age of >35 years are considered to be an important risk factors and have significant role in the development of congenital anomalies [10].

We aimed to study the occurrence of chromosomal abnormalities in infants and children with different phenotypic presentations and to analyze the impact of associated risk factors such as maternal age, consanguinity, family history of any congenital anomalies or malformations, and the predictive clinical indicators for chromosomal abnormalities in children. We hypothesized a significant association between the risk factors and for the presence of chromosomal abnormalities.

MATERIALS AND METHODS

This retrospective cohort study was conducted in King Hamad University Hospital, a JCI accredited tertiary care centre in Bahrain. The study included 112 children (aged 0–13 years) admitted to the pediatric department of our hospital from January 2017 to January 2020 and underwent karyotyping for different clinical indications such as dysmorphic features, congenital anomalies, symmetric intrauterine growth retardation, short stature, developmental delay, microcephaly, and neurological defects such as seizures and hypotonia. Karyotyping was performed for congenital anomalies such as congenital heart defects, limb anomalies, eye anomalies, ambiguous genitalia, cleft lip/palate, tracheoesophageal fistula, anorectal malformation, and abdominal defects. Children above 13 years and those previously admitted with diagnosed metabolic disorders were excluded from our study.

The data were collected retrospectively from electronic medical records and were entered into an Excel sheet for statistical analysis. The data included maternal age, consanguinity, family history of any congenital anomalies and malformation, clinical indicators, and the results of chromosomal analysis. The study was approved by the Institutional Research Board of King Hamad University Hospital, Bahrain. For cytogenetic analysis, 5 mL peripheral blood sample was collected from all the patients and stored in heparinized test tubes. Chromosomal analysis was performed on cultured lymphocytes within a culture medium in an incubator at 37°C for 72 h. G-banding with Trypsin and Giemsa was used to determine the karyotypes, and numerical as well as structural abnormalities were reported on at least 20 well-spread and well-banded metaphases after examination.

As there were not enough published data to estimate the desired prevalence of chromosomal abnormalities in Bahrain, we calculated the predicted prevalence for chromosomal abnormalities as 0.27 based on a pilot study conducted in Bahrain in 1996 [11]. The sample size of 320 was estimated for specificity of 80% with 95% confidence interval (CI) at 5% level of absolute precision [12]. However, our study was aimed to include all babies who underwent chromosomal analysis during the 3 years of the study period.

Data were analyzed using MedCalc® version 19.3. Mean and standard deviation were calculated for the age distribution of the study population. Pearson Chi-squared statistic >3.841 at degree of freedom (df=1) and an alpha level significance of 0.05 was

performed to find the association between risk factors and the outcome of chromosomal study. Fisher's exact test was used to find the association between risk factors and the outcome of karyotype study when the individual cell count values were <10. Relative risk (RR) with 95% CI was used to find the "times of risk" compared to those who do not have the risk factors for chromosomal abnormalities. $p < 0.05$ was considered statistically significant.

RESULTS

A total of 112 children had chromosomal analysis during the study period with the mean age of 19 months (Mean±SD: 19.22±38.82). There were 71 neonates (≤ 1 month) constituting 63.4% of the study population.

Out of 112 children, 37 (33%) had abnormal chromosomal study, which was a statistically significant finding ($p < 0.0001$) of our study. There was a significant difference between the frequency of children with structural and numerical abnormalities, with numeric abnormality being more significantly prevalent. There were 23 (62.2%) children with numerical abnormalities which was statistically significant ($p < 0.0001$). The most common numerical abnormality observed was trisomy 21. The risk of Down syndrome was found to be almost 2 times higher when compared to other chromosomal abnormalities (RR 1.94, 95% CI 1.42–2.66, $p < 0.0001$) of our study (Table 1). Among 37 children with abnormal chromosomal study, 14 (37.8%) had structural chromosomal abnormalities (Table 2).

The risk for chromosomal abnormality was shown to be lower in males compared to females, although there was no statistical significance (RR 0.87, 95% CI 0.63–1.21, $p = 0.43$).

Our study showed a statistically significant association between the presence of dysmorphic features and chromosomal abnormalities (Chi-squared 25.55, $p < 0.001$). Risk for chromosomal abnormality in children with dysmorphism was 3 times higher when compared to children with no dysmorphism (RR 3.06, 95% CI 1.71–5.50, $p = 0.0002$). Among the congenital anomalies, acyanotic congenital heart defects had a strong association with chromosomal abnormalities (Chi-squared 11.485, RR 1.43, 95% CI 1.10–1.86, $p = 0.0069$) (Table 3).

On analysis of associated risk factors, a strong association between chromosomal abnormalities and the maternal age of >35 years (Chi-squared 26.58, $p < 0.0001$) was observed. Risk for chromosomal abnormality in children born to mothers >35 years of age was 1.75 times more when compared to the children born to mothers ≤ 35 years age (Table 4).

A subgroup analysis on associated risk factors for Down syndrome showed a strong association for maternal age >35 years (Chi-squared 11.584, $p = 0.0007$). The risk for Down syndrome in children born to mothers >35 years of age was 3.5 times more than in children born to mothers ≤ 35 years age; however, the risk was 35% lower in the consanguineous parents (Table 5).

DISCUSSION

Chromosomal abnormalities are often the cause of early pregnancy loss, fetal malformations, and still birth. Several types

Table 1: Distribution of cases based on numerical chromosomal abnormalities

Numerical chromosomal abnormalities	Frequency	Percentage from abnormal karyotyping (n=37)	Percentage (%) from total chromosomal analysis (n= 112)	p value
Trisomy 21	18	48.6	16	<0.0001
Trisomy 18	2	5.4	1.8	
Turner syndrome	2	5.4	1.8	
Trisomy 13	1	2.7	0.9	

Table 2: Distribution of cases based on structural chromosomal abnormalities

Structural chromosomal abnormalities	Frequency	Percentage from abnormal karyotyping (n=37)	Percentage from total chromosomal analysis (n=112)
46, XY,22ps+	2	5.4	1.8
46, XYqh+	2	5.4	1.8
46, XX,16qh	2	5.4	1.8
46, XY,del(5)(p13.1.p.15.3)	1	2.7	0.9
46, XYdup(9)(q12q13)	1	2.7	0.9
46, XY9qH -Heterochromatic of ch9	1	2.7	0.9
46, XX,1qh	1	2.7	0.9
46, XY,dup(7)(q31.1q31.3)	1	2.7	0.9
46, XX,1qh+	1	2.7	0.9
46, XY,21ps+	1	2.7	0.9
46, XX,19qh, +22qh	1	2.7	0.9

Table 3: Clinical indicators for performing chromosomal analysis of the study population

Clinical indications	Frequency	χ^2 (df=1)	RR (95%CI)	p value
Dysmorphic features	47	25.553	3.06 (1.71 to 5.50)	0.0002
Neurological defects (seizures, microcephaly, hypotonia)	30	1.947	1.19 (0.91 to 1.55)	0.19
Congenital heart defects	22	11.485	1.43 (1.10–1.86)	0.0069
Developmental delay	21	1.117	1.11 (0.90–1.36)	0.32
Symmetric IUGR	14	2.52	0.88 (0.78–1.00)	0.06
Short stature	12	0.389	0.95 (0.84–1.08)	0.50

Table 4: Analysis on risk factors for chromosomal abnormalities (n=112)

Risk factors	Frequency	χ^2 (df=1)	RR (95%CI)	p value
Consanguinity	39	1.466	0.84 (0.64–1.09)	0.20
Family history of anomalies/malformations	18	0.001	1.00 (0.84–1.19)	0.97
Maternal age >35 years	21	26.58	1.75 (1.29–2.36)	0.0003

Table 5: Subgroup analysis on risk factors for Down syndrome (n=18)

Risk factors	Frequency	χ^2 (df=1)	RR (95%CI)	p value
Consanguinity	10	4.381	0.65 (0.42–0.98)	0.04
Family history of anomalies/malformations	6	0.654	0.88 (0.66–1.17)	0.41
Maternal age >35 years	18	11.584	3.55 (1.45–8.69)	0.0055

of genetic tests can identify chromosomal disorders, such as karyotyping, comparative genomic hybridization (array CGH), and fluorescence *in situ* hybridization. Cytogenetic analysis (karyotyping), utilized as the standardized tool in genetic counseling for the past few decades, is still the most available tool in many centers. Factors such as advanced maternal age (>35 years) can increase the risk for chromosome abnormalities in a pregnancy [13]. Thus, individuals or families concerned about an inherited condition may benefit from a genetic consultation [14].

Polipalli *et al.* in 2016 conducted a similar retrospective study to find the prevalence of chromosomal abnormalities in North Indian patients [15] and observed chromosomal abnormalities in 43.1% of their study population, whereas in our study, chromosomal abnormality was observed in 33% (p<0.0001) of the study population. Children aged from birth to 13 years were included (mean: 19.22±38.82 months), which is contrary to Polipalli *et al.* study which included individuals from birth to 37 years of age (mean: 7.9±8.1 years). Out of 112 children,

71 neonates (≤ 1 month) constituted 63.4% of the study population, whereas 29.8% of cases in their study consisted of children under the age of one. Similar to our study, a predominance of female gender 57.2% was observed in their study. However, to consider gender as a potential risk factor for chromosomal abnormalities, population-based data were a requirement for better assessment.

The risk for Down syndrome was found to be almost twice as compared to other chromosomal abnormalities (RR 1.94, 95% CI 1.42–2.66, $p < 0.0001$). A similar inference was observed by Polipalli *et al.* with occurrence for Down syndrome in almost 81.4% of the study population [15]. The reason for high occurrence of chromosomal abnormalities might be due to the legal prohibition of termination of pregnancies, even though advanced prenatal diagnostic techniques are available in the country.

A study by Caksen *et al.*, 2019, on 33 children with intellectual disabilities with the presence of chromosomal aberration established that 21% of the study population had structural chromosomal abnormalities; although it was not statistically significant enough to establish the cause for intellectual disability [16]. However, they recommended that chromosomal analysis has to be performed on children with intellectual disabilities. In our study, structural chromosomal abnormalities were observed in 37.8% of the children with an abnormal karyotype, but the intellectual disability of the study population was not included for the analysis.

Another retrospective study by Sadek *et al.*, 2018, on the yield of chromosomal study in children with global developmental delay and dysmorphic features demonstrated 61.1% of the sample size with abnormal karyotype [17]. Our study results were almost similar as it showed a statistically significant association between the presence of dysmorphic features and chromosomal abnormalities. On the other hand, although the developmental delay was found higher in children with chromosomal abnormalities, there was no statistical significance ($p = 0.32$). Sadek *et al.*, 2018, expressed Down's syndrome as the most common numerical abnormality (92.2%) of the study population [17].

Pandey *et al.* conducted a karyotype study on children with suspected case of Down's syndrome [18] and noted that 93% of children had trisomy 21, followed by Robertsonian translocation in 4.7% and mosaicism in 2.3%. Our study observed Down syndrome in 48.6% of the children with abnormal karyotype ($n = 37$) and all children were diagnosed as trisomy 21. Concerning maternal age, in Pandey *et al.* study, 55% were of > 35 years [18]. Our study also demonstrated a strong association between Down syndrome and maternal age of > 35 years ($p = 0.0007$). There was 3.6 times more risk of Down's syndrome in children born to mothers > 35 years of age than those born to mothers ≤ 35 years ($p = 0.0055$).

Cytogenetic analysis performed in different populations worldwide indicates that trisomy 21 is the most common variant of Down's syndrome, with incidence varying between 83.82% and 95.51% as reported by various authors [17-19]. The reported occurrence of Down's syndrome in our study based on the single-center data was 48.6%. Advanced maternal age was one of the most important risk factors contributing to the non-disjunction

of chromosome. The current study demonstrated a very strong association of advanced maternal age with the birth of a child with Down's syndrome, which has been proven by various studies [20-24]. The underlying mechanism is the long arrest of the oocytes in prophase I of meiosis. [25].

In relation to consanguinity, there was 35% lower risk for Down syndrome in the consanguineous parents (RR 0.65, 95% CI 0.42–0.98, $p = 0.04$), which was a similar finding to previous published literatures [26,27]. Shawky *et al.* observed a high incidence of consanguinity in autosomal recessive and multifactorial disorders (78.8% and 69.8%, respectively), whereas the incidence in chromosomal disorders was 29.1% [28]. However, recent research in 2018 by Ray *et al.* reported for the 1st time that consanguineous marriage was a novel risk factor for chromosome 21 non-disjunction in younger maternal age [29].

This study had a few limitations. The results of our study were derived from a single-center outcome data with a relatively small sample size. As our study sample size was inadequate, the study was underpowered to document the desired prevalence.

CONCLUSION

The occurrence of chromosomal abnormality was found to be high from our single-center outcome data. Our study highlights the role of cytogenetic analysis in children with dysmorphic features, congenital heart defects, and in children born to mothers with advanced maternal age (> 35 years). Cytogenetics is the gold standard, but definite diagnosis is achieved by molecular biology tests. We propose that genetic diseases and chromosomal disorders can be controlled by integrated and comprehensive efforts. Henceforth, a multicenter database research should be conducted in the future to find the desired prevalence of chromosomal abnormalities in Bahrain.

AUTHOR CONTRIBUTIONS

AA was the principal investigator, drafted the protocol, collected the data, did the initial analysis and drafted the initial manuscript. JJ edited the protocol, completed the analysis, interpreted the results, edited and drafted the final manuscript. ES supervised the aspects of the work. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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