

The Effect of Birth Order on Conditions Having Genetic Etiology

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KEYWORDS Mental retardation; multiple congenital malformation; bad obstetric history; female factors; male factors; birth order; genetic etiology

ABSTRACT Division of Human Genetics is the referral center for karyotyping and counseling. This particular investigation has been carried out as students project for a period of 2 months. Being a retrospective study the project has been done on 1000 consecutively referred cases with Mental Retardation, Multiple Congenital Abnormality, Bad Obstetric History (abortions and or livebirths) Male Factors (infertility, hypogonadism, ambiguous genitalia, Klinefelter syndrome), Female Factors (amenorrhea, Turner syndrome) and others (single gene disorders, syndromes, consanguinity, premarital counseling, multifactorial). In this investigation is reported, whether there is an association between birth order and the conditions for which the genetic etiology has been determined. It has also been attempted to find out the effect of birth order on the sex of the probands as well on the chromosomal abnormality. The gathered data from the detailed proforma was statistically analyzed with 'chi-square test'. Among the consecutively referred 1000 cases only in 790 cases complete information could be obtained, out of which the couples with BOH (365, 45.91%) have shown the highest referral followed by MR (142, 17.97%). The findings have suggested that the 1st birth order seemed to be associated to clinical conditions (304/ 790, 38.48%) ($p < 0.001$). Birth order has shown preference to live born females (417/ 790, 52.78%) ($p < 0.001$). 15% of the referred conditions had abnormal karyotype (120/ 790) and abnormal karyotype was not related to birth order ($p > 0.05$). Incidentally, the association between the chief complaints and consanguinity (223/ 790, 28.23%) was calculated and it was found to be significant ($p < 0.001$). In view of the absence of any other study based on such large size, it is opined that similar studies are in need to say with certainty, that there may be the effect of birth order on Mental Retardation, Multiple Congenital Abnormality, Bad Obstetric History, Male factors, Female factors and others.

INTRODUCTION

The conditions suspected to have genetic etiology (single gene disorders, chromosomal abnormality, multifactorial inheritance) are the Mental Retardation (MR), Multiple Congenital Abnormality (MCA), Bad Obstetric History (BOH) (couples who have had abortions and or livebirths), Male Factors (MF) (infertility, hypogonadism, ambiguous genitalia, Klinefelter syndrome), Female Factors (FF) (amenorrhea, Turner syndrome) and others (single gene disorders, syndromes, consanguinity, premarital counseling). In literature, information is available about birth order, parental age and Down syndrome and MR. Otherwise, there seemed to be paucity of information about the association of birth order to the conditions with genetic etiology.

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At Division of Human Genetics, as per the diagnosed condition, karyotyping and or counseling are offered. In view of the availability of the data, the present study has been undertaken so as to find out the correlation of birth order to the conditions with genetic etiology.

Aim

- 1) to find out the effect of birth order on the following conditions suspected with genetic etiology: MR, MCA, BOH, MF, FF and others (single gene disorders, syndromes, consanguinity, premarital counseling, multifactorial).
- 2) to find out the association between birth order and the sex of the probands.
- 3) to report the occurrence of abnormal karyotype.
- 4) to determine whether any association exists between birth order and abnormal karyotype.

MATERIAL AND METHOD

Division of Human Genetics is the center for karyotyping and counseling. This particular

investigation has been carried out as a project for a period of 2 months. Being a respective study, the information was gathered from the detailed duly filled proforma of 1,000 consecutively referred cases. The data has been tabulated as per the chief complaints for which the probands have been referred. The data was statistically analyzed with 'chi-square test'.

RESULTS

Among the consecutively referred 1000 cases only in 790 cases complete information could be obtained, out of which the couples with BOH (365, 45.91%) have shown the highest referral followed by MR (142, 17.97%) (Table 1)

Table 1: Chief complaints at the time of referral.

Complaints	Number	Percentage
MR	142	17.97
MCA	88	11.13
BOH	365	45.91
MF	125	15.82
FF	37	4.68
Others	33	4.17
Total	790	-

It is to be noted that for couples the male and female partners have been identified as individuals. Irrespective of the complaints the 1st born showed significantly a higher percentage of referrals (304/790, 38.48%) ($p > 0.001$) (Table 2).

The birth order effect in female probands (417/790, 52.78%) seemed to be significant ($p > 0.001$) (Table 3).

Abnormal karyotype was detected in 120 (28.23%) (Table 4) and birth order was not associated to the abnormal karyotype ($p > 0.05$ to 0.5).

Table 2: Chief complaints v/s birth order.

Chief complaints	Birth order				
	1 st	2 nd	3 rd	4 th +	Total
MR	67	38	28	09	142
MCA	45	28	09	06	88
BOH	126	104	67	68	365
MF	11	14	05	07	37
FF	42	34	25	24	125
Others	13	15	05	00	33
Total	304	233	139	114	790
Percentage	38.48	29.49	17.59	14.43	-

Chi square = 40.3; df = 15; $p < 0.001$ - significant.

Table 4: Chief complaints v/s karyotype.

Complaints	Normal	Abnormal	Total
MR	73	69	142
MCA	79	9	88
BOH	353	12	365
MF	29	8	37
FF	105	20	125
Others	31	02	33
Total	670	120	790
Percentage	84.81	15.189	-

Karyotype vs birth order:

1st birth order: Chi square 2.96; df 1; $p > 0.05$ - non significant

2nd birth order: Chi square 1.40; df 1; $p > 0.05$ - non significant

3rd birth order: Chi square 0.35; df 1; $p > 0.5$ - non significant

4th birth order onwards: Chi square 1.58; df 1; $p > 0.5$ - non significant

Incidentally, the association between and consanguinity (223/790, 28.23%) was calculated and it was significantly associated ($p < 0.001$).

DISCUSSION

From literature, it became apparent that this

Table 3: Chief complaints vs birth order vs sex of probands.

Complaints	Birth order								Total
	1 st		2 nd		3 rd		4 th +		
	m	f	m	f	m	f	m	f	
MR	43	24	20	18	18	10	05	04	142
MCA	22	23	17	11	08	01	04	02	88
BOH	57	69	52	52	34	33	38	30	365
MF	11	-	14	-	05	-	07	-	37
FF	-	42	-	34	-	25	-	24	125
Others	06	07	09	06	04	01	-	-	33
Total	139	165	112	121	69	70	54	60	790
%	17.5	20.8	14.1	15.3	8.7	8.8	6.83	7.72	

Chi square value - males (m) 26.69; df 12; $p > 0.05$ - non-significant

Chi square value - females (f) 22.54; df 12; $p < 0.001$ - significant

Table 5: Consanguinity v/s chief complaints.

Complaints	Consanguinity	Non-consanguinity	Total
MCA	48	40	88
MR	39	103	142
BOH	76	289	365
MF	6	31	37
FF	39	86	125
Others	15	18	33
Total	223	567	790

Chi Square = 49.38; d.f = 5; $p > 0.001$ Significant

might be the first study on the effect of birth order on several conditions with genetic etiology. These conditions mostly belong to the multifactorial mode of inheritance. Of course single gene defects and chromosomal abnormality have been determined to be the causal factors. Moreover, the birth order reflects the parental age at conception.

The chromosomal aspect of the genetic etiology in MR is around 22.5%, in MCA 6% and in BOH / male factors / female factors 5.5% (Rimoin et al. 2002; Turnpenny and Ellard 2005; Young 2005).

Among the conditions on which the study has been attempted MR may have single gene disorders as the cause, as part of the syndrome. Otherwise, the conditions i.e the chief complaints at the time of the referral belong to the multifactorial mode of inheritance, where poly-genic distribution with environmental contribution may be the factors.

Consanguinity is known for its association to MR, MCA, BOH, amenorrhea and hypogonadism (Bhat and Babu 1998; Bittles et al 1988; Bittles 2002). In India, the observed high range of consanguinity in population is 5 to 60% (Turnpenny and Ellard 2005).

PRESENT STUDY

Chief Complaints at the Time of Referral:

The higher percentage of referral for BOH and MR for karyotyping and counseling are expected. BOH is because of the size of the population in the individuals in the reproductive age and that too the anxiety to get normal off springs after undergoing the trauma with BOH. Mental retardation is also a common condition including its severe as well as the mild category, constituting 23.8 to 33.8% of the population (Young 2005). Among the male and female factors, the common referral is for amenorrhea and hypogonadism.

Chief Complaints v/s Birth Order: The association between birth order and the clinical conditions may be co-incidental. The reasons need to be looked in detail. The increased percentage of the referral of 1st born indicates the awareness to look for the genetic etiology and the options that need to be taken for the next conceptions. From 2nd birth order onwards, may be the previous birth was either normal or aborted or stillborn.

Chief Complaints v/s Birth Order v/s Sex of Probands: Association seen between first born and the female sex may be also a co –incidental finding. The association between 1st birth order female conceptions actually reflects younger parental age. It may also be stated that in spite of the younger maternal age any abnormal male conception may not be reaching the term.

The findings of the present investigation suggested that female conceptions irrespective of the conditions may be carried to term or there is a general tendency for male conceptions to be aborted or still born or may be there is a sequential ratio in the spermatogenetic process. The chances of Y bearing sperms reaching fertilization is less, naturally, more female conceptions are found. The higher the birth order, the higher the maternal age so any women with advanced age pregnancy may not be carrying male conceptions to term.

Specifically, in MR, the high number of male probands may be reflecting the X- linked mode of inheritance.

Chief Complaints v/s Karyotype and Karyotype v/s Birth Order: Chromosomal abnormality has been detected as the genetic etiology 15% of the referred conditions, even though the association of the birth orders to the karyotype was found to be non -significant. The reported incidence of chromosomal abnormality, the pooled incidence including the numerical and structural chromosomal abnormality for the autosomes and sex chromosomes is 99/ 10,000 live births (Turnpenny and Young 2005). The 15% (120/ 790) occurrence includes the numerical and structural abnormality of the chromosomes. The bias exists, because after almost ruling out the other causes, the probands are referred for karyotyping and counseling.

The prevalent normal karyotype indicated that the clinical conditions are not mainly due to the abnormalities in the chromosomes but may be due to multifactorial as well as non -genetic factors or the cause is not known.

Consanguinity and the Conditions i.e the Chief Complaints at the Time of Referral: The association of the consanguinity on the various conditions agrees with most of the findings in literature. In view of the presence of consanguinity, autosomal recessive mode of inheritance, one of the single gene mendelian pattern of inheritance has to be kept in mind. In consanguinity is the probability of the chances of the genes to be inherited in the homozygous condition. Then, it is natural that consanguinity may be influencing the formation of the conditions. The observations from the investigation could not be discussed further because of the non-availability of more or less similar investigations from the literature.

CONCLUSION

The effect of birth order to several clinical conditions requiring karyotyping as the base line investigation has been observed. Birth order seemed to have preference to live born female probands. The conditions are associated to abnormal karyotype as well as to the consanguinity. The conditions with normal karyotype

may be multifactorial and or non- genetic. Association between the birth order and abnormal karyotype could not be observed. This investigation, a pilot study has provided basic research information.

In view of absence of any other study of such large size, it is opined that similar studies are in need to say with certainty, that there could be the effect of birth order.

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