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Mental Retardation among Children Born with Birth Defects

Nargues M. Hassanein*

ABSTRACT: Mental retardation (MR) is a major health problem affecting 3% of the population. It results from the interaction of many genes and non-genetic factors. However, in up to 60% of patients the aetiology remains unclear. The aim of the study is to examine the association of birth defects and MR, taking into consideration the type of birth defect, level of MR, co-occurrence of MR with other developmental disabilities, genetic and biological risk factors. A case control study was conducted on 300 children with MR from December 2006 to December 2007. They were referred to the Human Genetics Department, Medical Research Institute, University of Alexandria, for diagnosis and genetic counseling. For comparison, 506 normal control groups were randomly selected. The cases were 156 males (54%) and 135 females (46%), the difference was not statistically significant. Out of 300 studied cases, 72 children (24%) had various chromosomal aberrations, while the remaining 228 (76%) had single gene disorder. From these groups 66 children had another coexisting DDS (25 with CP, 15 had VL, 10 with autism; 10 HL and 6 had epilepsy). Mild MR (MMR) was more prevalent among all the studied cases than severe MR (SMR), there was significant association between SMR and birth defects (OR= 1.85, CI: 1.05-3.27). Birth defects occurred in 180 children (40 children with Down syndrome, 1 with sex chromosomal defect, 3 with other chromosomal anomalies, and the remaining 136 with non-chromosomal abnormalities). There was significant association between children with Down syndrome and birth defects (OR=10; CI: 1-242.25). Birth defects were present in 41 children with MR and other coexisting DDs. Also, it was found that all children with different birth defects had significant association with MR, (OR= 87.21; CI: 40.38-196.31). These MR risks tended to be the largest among infants born with heart and central nervous system defects. There was significant association between low birth weight (OR = 3.57; CI: 1.91-6.65), preterm (OR= 9.63; CI: 2.21-47.84), and parental consanguinity (OR= 4.19; CI: 2.9-6.06) and the occurrence of MR. This study high-lights the role of prenatal factors in the origin of many DDS especially MR and suggests that a sizable proportion of DDS may be caused by insults occurring early in embryologic development.

INTRODUCTION

Developmental disabilities (DDs) comprise a group of non-progressive conditions manifested in childhood that result from insults to the developing brain or sensory organs and are associated with deficits in many areas of day-to-day functioning,

* Department of Human Genetics, Medical Research Institute, Alexandria university, Alexandria, Egypt

such as communication, learning behavior, and motor ability.[1]

The most serious of DDs (mental retardation (MR), cerebral palsy (CP), epilepsy, autism, bilateral hearing loss (HL), and visual loss (VL), affect 1% to 2% of young children.[2]

Mental retardation (MR) is a major health problem affecting 3% of the population. It results from the interaction of many genes and non-genetic factors such as prenatal infections, prenatal exposure to teratogenic substances, and perinatal asphyxia.[3] However, in up to 60% of patients, the aetiology remains unclear. Cytogenetically visible chromosomal aberrations account for almost 15% of all cases. Deletions and duplications that are too small to be detectable by conventional karyotyping seem to be equally important.[4]

Some structural birth defects other than those that directly affect the central nervous system, may play a role in the origin of some DDs.[5,6] Many epidemiologic studies found that children with structural defects are at increased risk for having MR in childhood.[4,7,8] These defects could serve as markers for early identification of children who eventually may need additional medical, educational, and social services.[7]

The aim of the study is to examine the associations of birth defects and MR, taking into consideration the type of birth defect level of MR, co-occurrence of MR with other developmental disabilities, Genetic, and biological maternal risk factors.

PATIENTS AND METHODS

A case control study was conducted from December 2006 to December 2007. The study included 300 children with MR attending the Human Genetic Clinic of Medical Research Institute (MRI), Alexandria University for diagnosis and genetic counseling.

Among the MR children studied, 66

cases had other coexisting developmental disabilities. From the 300 MR children, 180 children had 1 or more birth defects. All cases were subjected to:

1. A detailed genetic sheet including parental consanguinity, parental age and history of previous births. Family history was ascertained for similar cases. Relevant perinatal events as: sex, plurality (singleton or multiple), gestational age and birth weight (<2500 or ≥2500 g) were collected. Maternal factors were studied including age at delivery, parity and detailed pregnancy history.
2. Full clinical examination with special attention to the major birth defects was done for each case.
3. A family pedigree was constructed for all cases.
4. Genetic laboratories tests including: cytogenetic studies, DNA studies using RT-PCR technique for fragile X-syndrome, biochemical screening tests and thin layer chromatography were done when needed for proper diagnosis.
5. Intelligence quotient (IQ) score was performed to all cases.

   The children were subdivided into 2 groups using the commonly defined categories of mild MR (IQ 50-70) and severe MR (IQ<50).
6. Other investigations were performed when necessary to reach the final diagnosis such as: ultrasound, X-ray, Echocardiography Electroencephalography (EEG), Electromyography (EMG), Audiogram, Fundus examination, and TORCH tests.
7. A control group of 506 cases of matched age and sex were randomly selected during the study period from the general population, providing they were free from any history of MR.
8. Statistical analysis was performed using the Statistical Package of Social Sciences. [SPSS] version 9.0 and Epinfo, version 6.04. Comparison of

quantitative data was done by chi-square test. Odds ratio values were determined for the risk factors (Sex, Low Birth Weight, Gestational age, Plurality, Positive Consanguinity, Maternal age, and Parity).

RESULTS

This study included 300 children with MR, their age ranged from 3 to 10 years. They were 165 males (54%) and 135 females (46%), from which 180 children (60%) were born with one or more birth defects. Birth defects were more frequent among the MR cases than the control group, $X^2 = 348.38$, $p \leq 0.00$. Table (1).

Out of 300 studied cases, 72 children (24%) had various chromosomal anomalies, while the remaining 228 children (76%) had single-gene disorders. Within this group, 66 children had another coexisting DDs (25 CP, 15 with VL, 10 had autism, 10 had HL and 6 with epilepsy), Table (2). Mild MR (MMR) was more frequent among all the studied cases than severe MR (SMR). Also, it was more frequent in children with birth defects (43.88% with isolated MR and 17.78% with coexisting MR), compared to SMR (31.67% and 6.67%, respectively). However, there was significant association between SMR and birth defects [OR = 1.85; CI: 1.05-3.27]. Table (3).

Birth defects occurred in 60% (180 children) of the cases (40 children with Down syndrome; 1 with sex chromosomal defect, 3 with other chromosomal anomalies, and the remaining 136 with non-chromosomal abnormalities). There was significant association between children with Down syndrome and birth defects (OR=10; CI: 1-242.25). Table (2). Birth defects were present in 62% of children with MR and other coexisting DDs (41 children), where it was more frequent in children with MR and visual loss. Also, it was found that all children with different birth defects had significant association with MR, (OR = 87.21; CI: 40.38-196.31).

These MR risks tended to be the largest among infants born with heart and central nervous system defects, Table (1)

The genetic and biological risk factors for MR in children with major birth defects were shown in table (4). There were significant associations between low birth weight (OR=3.57; CI: 1.91-6.65), preterm (OR = 9.63; CI: 2.21-47.84), and parental consanguinity (OR = 4.19, CI: 2.9-6.06) and the occurrence of MR. The other biological risk factors (sex plurality, maternal age, and parity) did not have a significance influence on the occurrence of MR.

Table (1): Distribution of Birth Defects among children with MR and the control group.

Defects	Children with MR		Control	
	No.	%	No.	%
1- Cardiovascualr system	45	25%	4	0.8%
2- Ear, Head, neck	32	17.79	-	-
3- Nervous system defects	27	15	2	0.4
4- Eye	20	11.11	-	-
5- Sex organ	15	8.33	-	-
6- Mixed birth defects	15	8.33	-	-
7- Musculo skeletal anomalies	9	5.0	2	0.4
8- Limbs anomalies	7	3.89	-	-
9- Gastro-intestinal anomalies	4	2.22	-	-
10- Urinary tract anomalies	4	2.22	-	-
11- Skin	2	1.11	-	-
Total	180	100	8	1.6

- **OR** = 87.21; CI: 40.30 – 196.31
X2 = 348.38; P $\leq$ 0.000

Table (2): Distribution of mental retardation in children with or without birth defects.

Etiology	Children with birth defects		Children without birth defects		Total	OR	95% CI
	No.	%	No.	%			
- Chromosomal abnormalities		61.11		38.89			
Down syndrome	40	55.55	20	27.78	60	10	(1-242.25)
Sex chromosomal anomalies	1	1.39	5	6.94	6	0.11	(6.00-1.15)
Other chromosomal anomalies	3	4.17	3	4.17	6	0.6	(0.04-4.19)
- Single gene disorders		59.65		40.35			
Isolated MR	92	40.35	70	30.70	162		
Coexisting MR	44	19.30	22	9.65	66	0.66	(0.35-1.25)

Table (3): Classification of MR according to the degree of IQ in children with or without major birth defects.

	Mild		Severe		OR	95% CI
	Isolated MR	Coexisting DDs*	Isolated MR	Coexisting DDs		
- Children with birth defects	79	32	57	12	0.41	(0.18-0.91)
-Children without birth defects	72	12	26	10	2.19	(0.79 - 6.11)

DDs: developmental disability

Table (4): Genetic and Biological risk factors of MR in children with birth defects.

Risk factors	Children with major birth defects		Control		Odds ratio	95% CI
	No.	%	No.	%		
1-Chromosomal abnormalities (n = 72)	**44**	61.11	-	-	-	-
Down syndrome (n = 60)	40	55.55	-	-	-	-
Sex chromosomal anomalies (n = 6)	1	1.39	-	-	-	-
Other chromosomal anomalies (n = 6)	3	4.17	-	-	-	-
2-Non chromosomal abnormalities (n = 228)	**136**	59.65	-	-	-	-
Isolated MR (n = 162)	92	40.35	-	-	-	-
Coexisting MR (n = 66)	44	19.30	-	-	-	-
3- Sex						
Male	97	54	253	50	-	-
Female	83	46	253	50	1.17	0.82-1.67
4- Low birth weight	21	11.67	30	5.9	3.57	1.91-6.65*
5- Gestational age:						
- Full term	177	98.33	498	98.4	-	-
- Preterm	3	1.66	8	1.6	9.63	2.21-47.84*
6- Plurality						
- Singleton	174	96.67	491	97	-	-
- Multiple	6	3.33	15	3	0.89	0.32-2.60
7- Positive consanguinity	92	51.11	121	23.9	4.19	2.9-6.06*
8- Maternal age:						
< 25	85	47.22	121	23.9	-	-
25-35	63	35	331	65.4	0.27	0.18-0.41
> 35	32	17.78	44	8.7	0.09	0.03-0.27
8- Parity						
Mutipara	130	72.22	466	88.1	-	-
Primipara	50	27.78	60	11.9	0.03	0.02-0.07

a = x^2 = 20.15 P ≥ 0.000
b = x^2 = 14.96 P ≥ 0.000
c = x^2 = 68.14 P ≥ 0.000
* statistically significant

DISCUSSION

Mental retardation (MR) refers to a clinical state that is developmental in origin and which affects intellectual and social functioning.[9] A specific cause for MR can be identified in approximately 80% of people with SMR and 50% of people with MMR.[10] Chromosomal abnormalities account for 35-40% of MR. They always cause syndromes of multiple congenital anomalies and MR.[11] Down syndrome remains the most important single cause of MR[12]. Other numerical and structural aberrations are far less common.[4]

In the present study, cytogenetically visible chromosomal aberrations were detected in 24% of cases with mild and severe MR. This may be attributed to the difference in methodology used in chromosomal analysis, also deletions and duplication that seem to be important cause, are too small to be detectable by conventional karyotyping. So, a proportion of our cases may have undetected chromosomal anomalies.

Gephardt in 2003,[13] reported that children with non-chromosomal defects (single gene disorders) even defects not involving the central nervous system had substantially increased risk for MR. In this study, single gene disorders were present in 76% of the cases (136 children).

Males were more likely to have MR than females in this study, although the difference was not statistically significant. Same results were obtained by previous studies[14,15]. It was reported that X-linked gene defects are though to be responsible for ~10% of MR found in males. [16]

In the present study, 180 children with MR had different types of birth defects. These findings are consistent with previous investigations that found children with different structural birth defects were at greater risk (8 and 27 folds, respectively) for being diagnosed as having DDs including MR in early childhood[7,17] . However, our observed risk was larger (87

folds), which may be due to differences in study design, including differences in population and case eligibility criteria.

Elevated risk of MR among children with birth defects indicates that the causes of MR may differ between those children who are born without birth defects. Such observations specifically provide evidence to suggest a prenatal cause for MR when there is co-occurrence. Taken together with the hundreds of studies that have identified specific syndromes that include MR and 1 or more birth defects as phenotypic components (e.g., Mowat-Wilson[18] and Hennekam[19] syndromes) elevated risks suggest that MR and birth defects may be pathogenetically related. This relationship may be causal (e.g., a specific birth defect causes MR), temporal (e.g., deleterious event or teratogen caused birth defect and MR), or genetic (e.g., a gene or genes caused the birth defect and MR) or may be characterized by multiple causal pathways and mechanisms. [17]

In the present study, risk factors which have shown significant association with MR were low birth weight, preterm, and parental consanguinity. Similar results were reported in pervious studies.[8,15]

In several studies, parental consanguinity was identified as another important etiologic factor, which is supported by the finding that inbreeding is associated with reduced cognitive performance. [20,21]

The other biological risk factors (maternal age at delivery and parity) did not have a significant influence on the occurrence of MR. These results were different from those obtained in previous study[8,22] who found increased risk for both mild and severe MR associated with increasing maternal age and for multiple births. This difference may be attributed to the difference in the population studied.

CONCLUSION

This study high-lights the role of prenatal factors in the origin of many DDs especially

MR and suggests that a sizable proportion of DDs may be caused by insults occur early in embryologic development. Because many cases of DDs are not manifested until months or years after birth, both the type and the number of birth defects present in the first year of life may serve as a marker or early warning sign of subsequent cognitive, motor, and sensory deficits.

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