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Socio-economic risk factors of mental retardation without a common genetic cause: inferences from population cohort study in Himachal Pradesh

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Abstract: **The current retrospective study was aimed to examine major risk factors of mental retardation without a common genetic cause to educate the population and define intercession methods. A total of 150 MR of unknown etiology and 150 normal children were included in this study and look over for stigmata of dysmorphology, malformations, growth retardation, family history of MR, developmental delay etc. Stanford-Binet Intelligence test was conducted for each participant. Mental retardation is found to be associated with maternal education, low birth weight, preterm birth, microcephaly, multiple births, male preponderance, rural origin etc. No maternal age effect was noticed in these individuals as most of the cases were born to younger mother but in severe mental retardation, risk increased consistently and independently with increasing maternal age. Birth order does not predict mental retardation of unknown etiology. Only severely affected individuals were associated with multiple births. Present study is a preliminary step towards revealing the subtle causes of mental retardation in population of Himachal Pradesh. This study exposes the current situation and identifies the most tenacious intrusions to reduce the occurrence of childhood MR in Himachal Pradesh. Proper monitoring of risk factors could prevent our human health system from a serious lifelong disability and burden of the society could be reduced.**

Keywords: **Maternal age effect, maternal education, order in sibship, microcephaly**

I. INTRODUCTION

Mental retardation is a cognitive disability that presents in infant stage or the early childhood years but cannot be diagnosed until the child is older than 5 years, when standardized measures of intelligence become reliable and effective. The American Association on Mental Retardation defines mental retardation by measures of three domains: intelligence (IQ), adaptive behavior, and systems of supports. Thus, one cannot rely solely on the measure of IQ to define mental retardation. Mental retardation (MR) is a severe and lifetime disability that has distressing effects on people and the health system. About 3% of children worldwide marked some degree of MR [1]-[3], although estimates vary with the demographic and socioeconomic composition of study populations [4], [5] and with definitions and study design [6]. The proportion of cases that can be attributed to a known cause is estimated to be only 30% to 50% [7], according to an estimate 18.6% to 44.5% of cases have exogenous or non-genetic causes and 17.4% to 47.1% have genetic causes [8], [9]. Inspite of comprehensive evaluation, the etiology could not be determined in 30–

50% of cases [10]. An understanding of the epidemiology of MR of unknown cause may lead to the identification of characteristics that might be direct causal factors or lie somewhere along the causal path. We report here an investigation of selected maternal and infant characteristics with mild, moderate, severe and profound MR of unknown cause among 150 imbeciles.

SUBJECTS AND METHODS

This study was conducted on 150 children diagnosed with MR of unknown etiology and 150 control group from various districts of Himachal Pradesh. Stanford-Binet test of intelligence was performed for assessing the intelligence quotient and all MR cases were classified into mild, moderate, severe and profound individuals having IQ values as:50-55 to 70 (mild), 35-40 to 50-55 (moderate), 20-25 to 35-40 (severe) and <20-25 (profound). A Performa, which incorporated their clinical features, sex of individuals, maternal age, maternal education, birth order, birth weight, preterm birth, plurality, microcephaly, pedigrees up to three generations etc. was filled for each patient after consulting their parents.

Statistical treatment: The data was analyzed using statistical techniques like frequency, mean, percentage and significance of differences between mentally retarded and normal individuals was evaluated by chi square test. P values below 0.05 were considered statistically significant.

Results: This study cohort included 150 children diagnosed with MR of unknown etiology from various places of

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Himachal Pradesh with a mean age of 14. 5 years (range: 10–17 years). Among all children with a diagnosis of MR of unknown cause, males outnumbered females at a ratio of 2.6:1. Compared with all live births, children with MR of unknown cause were more likely to have a birth weight <2500 gm, be singleton (78%), microcephalic (58%) and first born (67.33%) (Table1) as compared to normal individuals. The mothers of children with MR of unknown cause were more likely to be born in rural area (76%) and have less than a high school education (68%) (Table1). All these associations were found to be significant having p values less than 0.05 (Table 1) except birth order with p value greater than 0.05 i.e. non-significant. Maternal age effect was not observed in mentally retarded individuals as most of MR individuals were born to mothers having maternal age ranged from 21-30 years and p values are also more than 0.05, this reveals that there is no significant difference in the occurrence of mental retardation in different maternal conception age groups in comparison to control group (Table 1). Average maternal age was similar for children with MR (27 ± 5.7 years) and normal individuals (27± 5.1years). Delivery at non-optimal gestational age is associated significantly with greater risk of mental retardation (30.67%) in comparison to normal individuals. (Table1). A spurious association was found in between maternal religion and mental retardation as p value was greater than 0.05. Pedigree analysis concluded that majority of MR cases (96%) were of sporadic type and most predominant mode of inheritance was X-linked recessive in familial cases (5%).

Increased risk for mild MR was observed for males (sex ratio is 2.8:1), normal birth weight children, singleton, first – second born children, and children whose mothers were <30 years of age at delivery, had less than a high school education, were born in rural area (Table 2). Risk evaluations for severe MR were elevated for males (sex ratio 2.3:1) and low birth weight children. Possibility increased steadily and autonomously with increasing maternal age and decreasing level of maternal education (Table 2). Increased risk was observed for children with rural mothers, compared with children with urban (Table 2). No excess in risk was observed for multiple births, for second- or later-born children (Table 2). Older maternal age was associated with increased risk of severe mental retardation (Table 2). This age effect was only seen in the lowest education group (Table 4) and was found to be significant having p values lesser than 0.05.In moderate and profound mental retardations, increased risk was observed for males (sex ratio for moderate MR is 2.3:1, sex ratio for profound MR is 1.5:1), first or second birth orders and those who were born to younger mothers of rural areas. Difference was found in frequencies of birth weight and maternal education, in moderate MR, most of cases had birth weight > 2500gm and was born to educated mothers (Table 3).

Table: 1. Percentage distribution of different variables in population cohorts of mentally retardedand normal individuals

Characters		MR individuals (N=150)		Control group (N=150)		χ^2 value	Sig.
		N	%	N	%		
Preterm births		46	30	2	1.33	48.02	<0.0001
Plurality	Singleton	117	78	149	99.33	19.39	<0.0001
	Multiple Birth	33	22	1	0.67		
Maternal Age	< 20 21-24 24-30 30-34 34=<	16 68 44 13 9	10.67 45.33 29.33 8.67 6	27 48 58 13 4	18 32 38.6 6.67 2.67	10.11	0.08
Birth place	Rural Urban	114 36	76.00 24.00	86 64	57.33 42.67	11.76	0.001
Microcephaly		87	58.00	3	2.00	112	<0.0001
Maternal Religion	Hindu Muslim	148 2	98.67 1.33	150 0	100 0.00	2.013	0.489
Body wt after birth	<2500gm >2500gm	78 72	52.00 48.00	10 140	6.67 93.33	63.17	<0.0001
Maternal education	<high school Graduate Post graduate	102 28 20	68.00 18.67 13.33	48 68 34	32.00 45.33 22.67	39.73	<0.0001
Order in sibship	1 2 >3	101 42 7	67 28 4.67	96 39 15	64 26 10	3.15	0.21

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Table: 2. Frequency of various variables in mild and severe mental retardation in comparison to normal individuals

Characters		Mild MR (N=115)		Control group (N=150)		χ^2 value	Sig.	Severe MR (N=20)		Control Group (N=150)		χ^2 Value	Sig.
		N	%	N	%			N	%	N	%		
Preterm births		26	22.6	2	1.33	31.18	<0.0001	18	90	2	1.33	133	<0.0001
Plurality	Singleton	102	88.70	149	99.33	212	<0.0001	1	5	149	99.33	151.3	<0.0001
	Multiple	13	11.30	1	0.67			19	95	1	0.67		
Maternal Age	< 20	12	10.43	27	18	8.21	0.08	2	10	27	18	33.31	<0.0001
	21-24	55	47.83	48	32			6	30	48	32		
	24-30	39	33.91	58	38.66			1	5	58	38.66		
	30-34	6	5.22	13	8.67			5	25	13	8.67		
	34=<	3	2.61	4	2.67			6	30	4	2.67		
Birth place	Rural	87	75.60	86	57.33	9.64	0.002	17	85	86	57.33	5.65	0.017
	Urban	28	24.30	64	42.67			3	15	64	42.67		
Microcephaly		57	49.56	3	2.00	84.08	<0.0001	18	90	3	2.00	126	<0.0001
Maternal Religion	Hindu	113	98.26	150	1000	219	<0.0001	20	100	150	100	NA	NA
	Muslim	2	1.74	0				0	0	0	0		
Body wt after birth	<2500gm	516	44.35	101	6.679	52.16	<0.0001	20	100	10	6.67	105.8	<0.0001
	>2500gm	4	55.65	40	3.33			0	0	140	93.33		
Maternal education	< high school	84	73.04	48	32.00	47.25	<0.0001	15	75	48	32	14.15	0.001
	Graduate	14	12.18	68	45.33			4	20	68	45		
	Post graduate	17	14.78	34	22.67			1	5	34	22		
Order in Sibship	1	78	67.83	96	64	5.68	0.058	14	70	96	64	0.35	0.84
	2	34	29.56	39	26			4	20	39	26		
	>= 3	3	2.61	15	10			2	10	15	10		

Table: 3. Frequency of various variables in moderate and profound mental retardation in comparison to normal individuals

Characters		Moderate MR (N=10)		Control group (N=150)		χ^2 value	Sig.	Profound MR (N=5)		Control Group (N=150)		χ^2 Value	Sig.
		N	%	N	%			N	%	N	%		
Preterm births		2	20	2	1.33	13.4	<0.0001	0	0	2	1.33	0.07	0.79
Plurality	Singleton	9	90	149	99.33	151.3	<0.0001	5	100	149	99.33	0.03	0.85
	Multiple	1	10	1	0.67			0	0.00	1	0.67		
Maternal Age	< 20	1	10	27	18	1.73	0.79	1	20	27	18	1.37	0.85
	21-24	5	50	48	32			2	40	48	32		
	24-30	3	30	58	38			1	20	58	38		
	30-34	1	10	13	8			1	20	13	8		
	34=<	0	0	4	2			0	0	4	2		
Birth place	Rural	7	70	86	57.33	1.42	0.23	3	60	86	57.33	0.01	0.91
	Urban	3	30	64	42.67			2	40	64	42.67		
Microcephaly		9	90	3	2	104.6	<0.0001	3	60	3	2	43.7	<0.0001
Maternal Religion	Hindu	10	100	150	100	NA	NA	5	100	150	100	NA	NA
	Muslim	0	0	0	0			0	0	0	0		
Body wt after birth	<2500gm	4	40	10	6.67	13.05	0.006	3	60.	10	6.67	17.91	0.004
	>2500gm	6	60	140	93.33			2	40	140	93.3		
Maternal education	< high school	1	10	48	32	7.63	0.02	2	40	48	32	1.42	0.52
	Graduate	9	90	68	45.33			1	20	68	45.3		
	Post graduate	0	0	34	22.67			2	40	34	22.6		
Order in sibship	1	6	60	96	64	0.88	0.88	3	60	96	64	0.55	0.61
	2	3	30	39	26 0			1	20	39	26		
	>=3	1	10	15				1	20	15	10		

Table: 4. Association between maternal age and education in severe mental retardation

S NO	Maternal age	<higher maternal education in severe MR cases (N=15)		<higher maternal education in normal (N=48)		χ^2 Value	Sig.
		N	%	N	%		
1	< 20	1	6.67	16	33.33	4.12	0.06
2	21-24	3	20	23	47.92	3.67	0.06
3	24-30	0	0	`7	14.59	2.46	0.18
4	30-34	5	33.33	1	2.08	12.95	0.002
5	34=<	6	40	1	2.08	16.35	<0.0001

Discussion: The present study was set out to shed more light on the factors driving such high incidence of MR in this region. Based on the current literature on MR, this study was focused on these parameters like maternal age, religion, maternal education, birth order, plurality, preterm births, low birth weight, sex ratio, and microcephaly with respect to normal individuals. All parameters were scanned in various degree of mental retardation i.e. mild, moderate, severe and profound with special emphasis on mild and severe mental retardation. .

Hitherto, it was held that risk of mental retardation increases with maternal age [11], [12]. But present study is in sharp contrast to previous ones, no maternal age effect was found in mentally retarded individuals. Majority of MR individuals were born to mothers in age group 21-24 years. This observation is concordant with many studies documented so far [13-15]. This might be due to competing nutritional needs of mother and the foetus, lack of family structure or lack of economic resources [16]. Our observation of an increased risk associated with advanced maternal age of severe MR contrasts a study which demonstrated an advanced maternal age effect only among children with mild mental retardation [17]. Whereas a study done in Atlanta [18] which grouped mildly and severely affected children together, a markedly elevated risk for MR occurring with other age-related disabilities was detected among older women. However, the increase in risk for severe MR associated with increased maternal age in our data is essentially considerable, proposing that concealed biological or non-biological aspects that covary with maternal age may increase risk for severe MR. Maternal education was found associated with risk for both mild and severe MR in this study and older maternal age effect was only seen in the lowest education group. This finding is in line with results from a study, which also documented a strong inverse association between maternal education and prevalence of

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MR in children without other neurologic conditions [19-20], [15]. In terms of risk for the population, it was older mothers with less than higher education whose births were associated with the greatest proportion of severe mental retardation. From a public policy point of view, children born to mothers with low level of education are an important group to target for prevention/early intervention efforts [19].

Birth order was also found to be a non-significant factor for mental retardation which is consistent with many reports [15], [21], [13]. Low birth weight was the strongest predictor of MR, both for mildly and severely affected children, a finding that confirms some previous studies. Among a population of French children with severe MR, low birth weight increased risk only among those children who also had cerebral palsy [22]. Data from a Finnish population-based study showed no significant difference in the proportion of low birth weight between children with MR and healthy children [23]. Consistent with our observations, 20% of children in the Atlanta population with no reported biomedical cause for their MR were of low birth weight [24]. In a study, a twofold to fourfold increased risk for MR was observed in association with low birth weight after children with other developmental disabilities were excluded [25]. Even though considerable changes in neonatal management, our data indicates that the smallest infants are still at augmented risk for emerging both mild and severe MR.

While it is known that children born preterm (<37 completed weeks) are at greater risk of intellectual disability than those born at full term [26-29], this information is reconcilable with our results. In present study, we examined the associations between gestational age and intellectual disability without a common genetic cause and found that 46 (30.67%) were born before completion of gestation age. This frequency is quite less in normal individuals (1.33%).
Significance of microcephaly was also observed in mentally retarded as well as normal individuals and it was observed that 87 (58%) patients were microcephalic in comparison to normal individuals having frequency only 2%. This information is in accordance with previous reports [30-32].

As compared to normal, prevalence of multiple births was greater in mentally retarded individuals which delineate its association with mental retardation and this result is concordant with a previous report [33]. Most of the observed increased risk for MR among twins was explained by their lower birth weight distribution. Multiple births were at slightly increased risk for severe MR only as compared to other degrees of MR. This finding is consistent with a previous report [34]. In present study, mental retardation was found more in Hindus (98.7%) than in Muslims (1.3%), this information is in accordance with previous studies [35], [15]. This might be due to the reason that Himachal Pradesh has less Muslim's population than Hindus. Moreover, sample size was small and areas were restricted to certain regions of Himachal Pradesh having large population of Hindus. Prevalence of mental retardation was found greater in cases which belong to rural area as compared to urban region which is in conformance with previous reports [36-37]. In the present study, preponderance of male was found to be more towards mental retardation [38]. Due to accumulation of intelligence genes on X-chromosome, it can be speculated that the possibility of MR and exceptional intelligence is more frequent in males [39]. Various factors in the child's environment due to socioeconomic condition of the family contribute to intellectual development of the child.

CONCLUSIONS:

Our study is irreplaceable in that it focused on identifying epidemiologic characteristics of unexplained MR in a population-based sample of children with MR in all levels of severity and is first report in this context from Himachal Pradesh. Although there is some degree of under ascertainment and misclassification of diagnosis in our study but the strength of the observed associations and the consistency of our results with previous reports suggest that the connotations with these sociodemographic and socioeconomic factor operating separately or synergistically are valid. Moreover, they provide information for understanding the fundamental causes of mental disorder and suggest that both biological and social factors are important. These factors will play an important role in the etiologic diagnosis which is important for providing evidence about pathogenesis, diagnosis, and recurrence risk and special medical intercession.

Abbreviations: MR: mental retardation, IQ: intelligence quotient, Sig.: significance, gm

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