The Epidemiology of Mental Retardation of Unknown Cause

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ABSTRACT. *Objective.* **To describe selected infant and maternal characteristics for children with mild and severe mental retardation (MR) of unknown cause.**

Study Design. **Children with MR of unknown cause born in California between 1987 and 1994 were identified through service agency records and compared with the total population of California live births for selected characteristics recorded on the birth certificate.**

Results. **For both children with mild and severe MR, risk was increased among males, low birth weight children, and children born to women of black race, older age at delivery, and lower level of education. Increased risk for mild MR was found for multiple births, second or later-born children, and children whose mothers were born outside of California. Increased risk for severe MR was observed among children born to Hispanic mothers; children born to Asian mothers also had increased risk for severe MR but decreased risk for mild MR.**

Conclusions. **These results provide clues for understanding the underlying causes of MR and suggest that both biological and social factors are important.** *Pediatrics* **2001;107(6). URL: http://www.pediatrics.org/cgi/content/full/107/6/e86;** ***sociodemographic factors; maternal age; developmental disability.***

ABBREVIATIONS. MR, mental retardation; DDS, Department of Developmental Services; CP, cerebral palsy; *ICD-9, International Classification of Diseases, Ninth Revision*.

Mental retardation (MR) affects ~1% of all school-aged children,[1] yet the proportion of cases that can be attributed to a known cause is estimated to be only 30% to 50%.[2] 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 pathway.

The majority of previous research describing the epidemiology of MR has focused on correlates for mild MR and severe MR, without differentiating between MR with or without an identified cause. These studies have led to the conclusion that mild MR is primarily related to social and environmental conditions and severe MR to underlying biological conditions.[3] A potential problem with these studies is that they generally assume that these identified risk factors apply equally to children with MR of known and unknown cause. Rarely have investigators questioned this assumption or focused specifically on those children with MR of unknown cause. In an attempt to address this concern, the Centers for Disease Control and Prevention conducted a study of sociodemographic risk factors for MR for subgroups of children defined by the presence or absence of other neurologic impairments.[4]

An alternative approach is to look for similarities in social and demographic characteristics among children with MR of unknown cause subclassified by level of MR severity. We report here an investigation of selected infant and maternal characteristics of children with mild and severe MR of unknown cause among the total population of over 4.5 million live births occurring in California over 8 successive years.

METHODS

The study population for this investigation included all children born in California between 1987 and 1994 whose mothers were California residents at the time of delivery (n = 4 590 333). Children in the study population with MR were ascertained from the California Department of Developmental Services (DDS), a statewide agency that coordinates diagnostic and remedial services for individuals with MR, autism, cerebral palsy (CP), epilepsy, and other neurologic conditions closely related to MR. Services are provided through a system of 21 locally based regional centers that receive referrals from primary care providers, educators, public health clinics, other service agencies, and parents. Eligibility is determined based on diagnostic parameters without regard to financial or citizenship status.

Children born between 1987 and 1994 and enrolled with DDS at any time between January 1, 1987 and July 7, 1999 with a diagnosis of MR at their most recent evaluation were identified from the service agency electronic data files (n = 27 547). MR is defined by DDS as "significantly subaverage intellectual functioning, existing concurrently with related limitations in at least 2 adaptive skill areas, and manifesting before age 18." Severity of MR is classified according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*) as mild (IQ = 50–70), severe (IQ < 50), or unspecified. To be eligible for services, diagnoses must be established by a physician or psychologist.

To identify California births, children with a diagnosis of MR were electronically linked to the California live birth certificate file using matching algorithms using name, date of birth, sex, county, and race/ethnicity. Questionable matches were manually reviewed (by L.A.C.). Of all children with a diagnosis of MR in the DDS files, 23 956 were successfully linked to a birth certificate and, therefore, eligible for inclusion.

California-born children with a diagnosis of MR of unknown cause without CP or autism were the participants of this investigation. Thus, children were excluded from all analyses if they had a diagnosis of CP or autism (n = 7221) or if their MR was attributed to chromosomal abnormalities (ICD 758.0–758.9; n = 4298), infections (ICD 001.0–139.9, 771.0–771.9; n = 115), endocrine or metabolic disorders (ICD 240.0–279.9; n = 135), injuries or poisonings (ICD 800.0–999.9; n = 204), or diseases (ICD 320.0–341.9; n = 139), anomalies (ICD 740.0–742.9; n = 688), or neoplasms (ICD 140.0–239.9; n = 42) of the central nervous system.

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Information on infant and maternal characteristics was obtained from California live birth certificate electronic files. Data on the gender of the child, birth weight, plurality, birth order, maternal age at delivery, self-identified maternal race/ethnicity, and maternal birthplace were available for children born in all study birth years. Data on level of maternal education at delivery were available for 1989–1994 births only.

The total live birth population for 1987–1994 (n = 4 590 333) was used as the denominator in rate calculations. Rate ratios (the ratio of the rate of disease [MR] among individuals exhibiting the study characteristic and the rate among those without the characteristic) and 95% confidence intervals were calculated to estimate the relative risk for MR associated with several infant and maternal characteristics. A multivariable Poisson regression model[5] was used to generate risk estimates for each characteristic, while simultaneously adjusting for all other characteristics under investigation.

RESULTS

In the study population of 4 590 333 California-born live births, 16 735 children were identified with a diagnosis of MR without CP or autism, representing a prevalence of 3.6 per 1000 live births. Of these, cause was known for 34% (n = 5621; prevalence of 1.2 per 1000) and unknown for 66% (n = 11 114; prevalence of 2.4 per 1000; Table 1). Among those children with MR of unknown cause and without CP or autism, 64% (n = 7115) had a diagnosis of mild MR, 20.3% (n = 2256) had a diagnosis of severe MR, and for 15.7% (n = 1743) severity was not specified (Table 1).

Among all children with a diagnosis of MR of unknown cause, males outnumbered females at a ratio of ~1.7:1 (Table 2). Compared with all live births, children with MR of unknown cause were more likely to have a birth weight <2500 g, be multiple births, and be third- or later-born (Table 2). Compared with mothers of all live births, the mothers of children with MR of unknown cause were more likely to be black, born in California, and have less than a high school education (Table 2). Maternal age was similar for children with MR compared with all live births. These patterns were similar for each of the 8 birth years of the study, despite fluctuations in overall prevalence.

Risk Factors for Mild MR

After adjustment for covariates in multivariate analyses, increased risk for mild MR was observed for males, low birth weight children, multiple births, second- or later-born children, and children whose mothers were 30 or more years of age at delivery, had less than a high school education, were born outside of California, or were black (Table 3). Decreased risk was observed for children born to Asian mothers; risk for children born to Hispanic mothers was similar to that for whites. Analysis of year of birth did not reveal any significant differences in these patterns.

Risk Factors for Severe MR

Adjusted risk estimates for severe MR were elevated for males and low birth weight children (Table 3). Risk increased consistently and independently with increasing maternal age and decreasing level of maternal education. Increased risk was observed for children with Hispanic, black, or Asian mothers, compared with children with white mothers, after adjustment in multivariate analyses (Table 3). No excess in risk was observed for multiple births, for second- or later-born children, or for children whose mothers were born outside of California. These patterns of risk were stable across birth years.

Risk Factors for MR of Unspecified Level

The adjusted risk profile for children with an unspecified level of MR was most similar to that observed for children with mild MR (Table 3) and was stable across the 8 birth years of the study.

DISCUSSION

In this population-based study of MR of unknown cause, based on over 4.5 million births in California during the late 1980s and early 1990s, children with mild MR and children with severe MR had similar patterns of increased risk associated with being male or being born weighing <2500 g. For both mild MR and severe MR, increased risk was associated with increasing maternal age and decreasing maternal education. In both groups of affected children, higher risk was observed for children born to black, compared with white mothers. Increased risk for children born to Hispanic mothers was observed only among children with severe MR; children born to Asian mothers also had increased risk for severe MR, but decreased risk for mild MR. Increased risk for mild MR was found for multiple births, second or later-born children, and for children whose mothers

TABLE 1. Cause of Mental Retardation Among Children Without Autism or Cerebral Palsy Enrolled With the DDS and Born in California Between 1987 and 1994

	Total (n = 16 735)		Mild MR (n = 9227)		Severe MR (n = 3465)		Unspecified MR (n = 4043)	
	n	(%)	n	(%)	n	(%)	n	(%)
Known cause	5621	(33.6)	2112	(22.9)	1209	(34.9)	2300	(56.9)
Chromosomal	4298	(25.7)	1575	(17.1)	801	(23.1)	1922	(47.5)
Infection/parasitic disease	45	(0.3)	17	(0.2)	16	(0.5)	12	(0.3)
Neoplasm	42	(0.3)	26	(0.3)	6	(0.2)	10	(0.3)
Endocrine or metabolic disorder	135	(0.8)	63	(0.7)	36	(1.0)	36	(0.9)
Disease of central nervous system	139	(0.8)	44	(0.5)	48	(1.4)	47	(1.2)
Central nervous system anomaly	688	(4.1)	247	(2.7)	224	(6.5)	217	(5.4)
Congenital infection	70	(0.4)	24	(0.3)	22	(0.6)	24	(0.6)
Injury/poisoning	204	(1.2)	116	(1.3)	56	(1.6)	32	(0.8)
Unknown cause	11 114	(66.4)	7115	(77.1)	2256	(65.1)	1743	(43.1)

TABLE 2. Characteristics of Study Population, California 1987–1994

	Live Births (n = 4 590 333)		MR of Unknown Cause (n = 11 114)	
	n*	(%)	n*	(%)
Child sex				
Male	2 350 287	(51.2)	7027	(63.2)
Female	2 240 020	(48.8)	4087	(36.8)
Birth weight				
<2500 g	274 419	(6.0)	2574	(23.2)
≥2500 g	4 314 859	(94.0)	8537	(76.8)
Plurality				
Singleton	4 489 348	(97.8)	10 520	(94.7)
Multiple	100 910	(2.2)	594	(5.3)
Birth order				
1	1 824 165	(39.7)	3685	(33.2)
2	1 412 612	(30.8)	3258	(29.3)
≥3	1 347 012	(29.3)	4148	(37.3)
Maternal age				
<20	533 319	(11.6)	1335	(12.0)
20–24	1 188 530	(25.9)	2833	(25.5)
25–29	1 352 240	(29.5)	3064	(27.6)
30–34	1 009 809	(22.0)	2462	(22.2)
≥35	504 751	(11.0)	1420	(12.8)
Maternal race/ethnicity				
White	1 884 556	(41.1)	4189	(37.7)
Hispanic	1 845 765	(40.2)	4239	(38.1)
Black	367 611	(8.0)	1650	(14.8)
Asian	267 685	(5.8)	518	(4.7)
Other	198 052	(4.3)	459	(4.1)
Maternal birth place				
California	1 812 955	(39.5)	5077	(45.7)
Other United States	883 320	(19.2)	2042	(18.4)
Mexico	1 088 144	(23.7)	2324	(20.9)
China	40 365	(0.9)	50	(0.4)
Japan	16 793	(0.4)	31	(0.3)
Vietnam	62 255	(1.4)	129	(1.2)
Philippines	95 031	(2.1)	202	(1.8)
Other	591 470	(12.9)	1259	(11.3)
Maternal education				
<High school	1 209 943	(34.1)	3322	(40.2)
High school graduate	1 074 594	(30.3)	2686	(32.5)
College	990 677	(27.9)	1846	(22.3)
Postgraduate	245 721	(6.9)	326	(3.9)

* Numbers may not add up to column total because of records with missing data.

were born outside of California; these factors were not associated with increased risk for severe MR. The risk associated with each of these factors was independent of the other factors and persisted across the 8 birth years of study.

The major strength of this study is the focus on MR of unknown cause in a population-based sample. The very large study population was possible because of the statewide, coordinated system of services provided to individuals with MR and other major developmental disabilities in California. Demographic data were obtained from vital statistics live birth files and, thus, not subject to recall bias or reporting differences among individual local agencies. Criteria for diagnosing intellectual disability and determining eligibility for services are primarily determined at the state level, although local differences inevitably exist, particularly with regard to enrollment of children at the milder end of the spectrum of disability.

Most individuals with severe MR become enrolled in the service system during early childhood, but children with mild MR, especially those with no other neurologic impairments, may never enter the system or may not do so until puberty. Because the youngest children in our study sample were only 4 years old, it is likely that children with mild MR were underascertained to a significant degree. However, the relative prevalence of MR among various sociodemographic groups in our study is similar to that reported in studies in which cognitive testing was conducted among all children in a given population,[6,7] indicating that our study sample, although incomplete, may be reasonably representative of the total population of children with MR.

The very large size of our study population prohibited validation of diagnostic information by either direct examination of the children or review of agency records. Local regional centers are required to schedule periodic evaluations with each client and to update relevant information; however, diagnostic information in the electronic client record is often limited to what was recorded at the time of initial intake and may not accurately reflect the most recent diagnosis. Data from a medical record review study of over 200 children enrolled in the DDS/regional center system revealed that although all children classified with severe MR according to the electronic data records did have some degree of MR, ~14% had a true diagnosis of mild MR.[8] We were unable to determine whether misclassification of severity was selectively influenced by the demographic characteristics of the child.

Misclassification of cause in the electronic files also occurs to an unknown degree. However, our finding of 77.1% unexplained cause among mildly affected children and 65.1% unexplained among severely affected children is similar to the 86.6% and 56.8% reported in Atlanta for mild and severe MR, respectively,[9] suggesting that such misclassification is unlikely to be substantial enough to affect the patterns of risk observed here.

Our study population was limited to children for whom a link to a California birth certificate could be made. Although some children who were excluded based on no link were most likely California births, they represent a small proportion of the total cases identified and, thus, are unlikely to bias our results in any substantial way.

Our observation of an increased risk associated with advanced maternal age for both mild and severe MR contrasts with data from Atlanta[4] that demonstrated an advanced maternal age effect only among children with mild MR. In a subsequent analysis of the Atlanta data, which grouped mildly and severely affected children together, a markedly elevated risk for MR occurring with other developmental disabilities was observed among older women; however, no maternal age effect was seen among isolated cases.[10] Our finding could be attributable to misclassification of children into the unknown cause group resulting from underreporting of conditions (eg, chromosomal anomalies) known to be associated with advanced maternal age and severe MR. However, the increase in risk for severe MR associated

TABLE 3. RR_cs and RR_as and 95% CIs for Mental Retardation and Several Infant and Maternal Characteristics, California 1987–1994

	Mild MR (n = 5028)*				Severe MR (n = 1536)*				Unspecified Level of MR (n = 1219)*			
	RR_c	95% CI	RR_a	95% CI	RR_c	95% CI	RR_a	95% CI	RR_c	95% CI	RR_a	95% CI
Child sex												
Female	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Male	1.9	1.8–2.0	1.9	1.8–2.0	1.3	1.2–1.5	1.4	1.2–1.5	1.6	1.4–1.8	1.6	1.5–1.8
Birth weight												
≥2500 g	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
<2500 g	4.9	4.6–5.2	4.3	4.0–4.6	4.3	3.8–4.9	4.3	3.8–4.9	5.6	5.0–6.4	5.4	4.7–6.2
Plurality												
Singleton	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Multiple	3.0	2.7–3.3	1.2	1.1–1.4	1.7	1.3–2.2	0.7	0.6–1.0	2.8	2.2–3.5	1.0	0.8–1.3
Parity												
1	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
2	1.2	1.1–1.2	1.1	1.1–1.2	1.1	1.0–1.3	1.1	0.9–1.2	1.1	1.0–1.3	1.2	1.0–1.3
≥3	1.6	1.5–1.7	1.3	1.2–1.5	1.5	1.3–1.6	1.1	1.0–1.3	1.6	1.4–1.9	1.5	1.3–1.8
Maternal age												
<20	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
20–24	0.9	0.9–1.0	1.1	1.0–1.2	1.1	0.9–1.3	1.3	1.1–1.6	0.9	0.8–1.1	1.0	0.8–1.2
25–29	0.9	0.8–1.0	1.1	1.0–1.3	1.1	0.9–1.3	1.4	1.1–1.7	1.0	0.8–1.2	1.0	0.8–1.2
30–34	0.9	0.9–1.0	1.3	1.1–1.4	1.1	0.9–1.4	1.6	1.3–1.9	1.2	1.0–1.4	1.1	0.9–1.5
≥35	1.0	0.9–1.2	1.4	1.2–1.6	1.4	1.2–1.8	1.9	1.5–2.4	1.2	1.0–1.6	1.2	0.9–1.5
Maternal education												
<High school	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
High school	1.0	0.9–1.0	0.7	0.7–0.8	0.8	0.7–0.9	0.7	0.6–0.8	1.0	0.8–1.1	0.8	0.7–1.0
College	0.7	0.6–0.7	0.5	0.5–0.6	0.6	0.5–.07	0.6	0.5–0.7	0.9	0.8–1.0	0.7	0.6–0.9
Postgraduate	0.4	0.3–0.5	0.3	0.3–0.4	0.4	0.3–0.6	0.4	0.3–0.6	0.8	0.6–1.0	0.7	0.5–0.9
Maternal birth place												
California	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
United States, not California	0.8	0.7–0.8	0.8	0.7–0.8	1.0	0.8–1.1	1.0	0.8–1.1	0.9	0.8–1.1	0.9	0.7–1.0
Mexico	0.7	0.6–0.7	0.6	0.5–0.6	1.2	1.1–1.3	0.9	0.8–1.1	0.7	0.6–0.8	0.8	0.6–0.9
Other	0.6	0.6–0.7	0.7	0.6–0.8	1.1	0.9–1.2	0.9	0.8–1.1	0.9	0.7–1.0	0.8	0.7–1.0
Maternal race/ethnicity												
White	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
Hispanic	1.0	0.9–1.0	0.9	0.8–1.0	1.4	1.3–1.6	1.2	1.0–1.4	0.9	0.8–1.0	0.8	0.7–1.0
Black	2.1	1.9–2.3	1.5	1.4–1.7	2.0	1.7–2.4	1.6	1.4–1.9	1.7	1.4–2.0	1.2	1.0–1.5
Asian	0.6	0.5–0.7	0.7	0.6–0.8	1.4	1.1–1.8	1.3	1.0–1.7	1.2	0.9–1.5	1.2	0.9–1.6

RR_c indicates crude rate ratio, RR_a, adjusted rate ratio, adjusted for all other variables in the table; CI, confidence interval.
* Only children with nonmissing values on all variables in the table are included.

with increased maternal age in our data is essentially linear and is substantial, suggesting that unidentified biological or nonbiological factors that covary with maternal age may increase risk for severe MR.

Low birth weight was the strongest predictor of MR, both for mildly and severely affected children, a finding that is inconsistent with some previous studies. Among a population of French children with severe MR who had been referred to a neonatal care unit, low birth weight increased risk only among those children who also had CP.[11] 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.[12] Results specific to children with isolated MR of unknown cause were not presented. Consistent with our observations, 20% of children in the Atlanta population with no reported biomedical cause for their MR were of low birth weight.[9] In a study conducted in Atlanta for children born in the mid 1970s, a twofold to fourfold increased risk for MR was observed in association with low birth weight after children with other developmental disabilities were excluded.[13] Despite substantial changes in neonatal management in the interim between that study and ours, our data indicate that the smallest infants are still at increased risk for developing both mild and severe MR.

Most of the observed increased risk for MR among twins was explained by their lower birth weight distribution. After controlling for birth weight and the other characteristics under investigation, multiple births were at slightly increased risk for mild MR only. This finding is consistent with data from Atlanta.[14]

Maternal education was associated with risk for both mild and severe MR in this study, independent of maternal race or other factors. This finding is consistent with results from the Atlanta study, which also demonstrated a strong inverse association, among both whites and blacks, between maternal education and prevalence of MR in children without other neurologic conditions.[15] Mean cognitive test scores in children have also been shown to be positively associated with maternal educational level.[15] Questions remain regarding the specific correlates of maternal education that are causally associated with MR, and when during prenatal or postnatal life they may be operating. If low maternal education is an indicator for socioeconomic disadvantage, our findings suggest that socioeconomic factors may be causally associated with some proportion of children

with severe MR. This is in stark contrast to the prevailing understanding that socioeconomic status has little or no association with severe MR, but it is the strongest and most consistent predictor of mild MR.[16]

The California data suggest ~50% increased risk for blacks for both mild and severe MR, with 20% to 30% increased risk for Asians and Hispanics for severe MR only. Although these risks are statistically independent of maternal education, it is not possible to determine the extent to which other socioeconomic factors are represented in these findings. It is also impossible to know whether differential reporting of severity level by race/ethnicity of the child or whether differential utilization of the service system by racial groups is affecting these results.

Our study is unique in that it focused on identifying epidemiologic characteristics of unexplained MR in a very large population-based sample of children with MR of all levels of severity. Although there is some degree of underascertainment and misclassification of diagnoses in our study population, the large sample size, the strength of the observed associations, and the consistency of our results with previous reports suggest that the associations with these sociodemographic factors are, in fact, valid. Furthermore, they provide us with clues for understanding the underlying causes of this common disorder and suggest that both biological and social factors are important. The next step is to identify specific factors that are correlated with the characteristics reported here and causally associated with MR.

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