Developmental Outcome in Children Exposed to Chloride-Deficient Formula

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ABSTRACT. The developmental outcome of 2- and 4-year-old children who had been exposed as infants to chloride-deficient formula was studied. A negative dose-response relationship was demonstrated between use of the formula without additional nutritional supplementation and cognitive outcome as measured by the Bayley Scales of Infant Development (Pearson $r = -.55$, $P = .01$) at 2 years of age. A similar negative relationship was demonstrated between this exclusive use of the defective formula and perceptual (Pearson $r = -.51$, $P < .05$), motor (Pearson $r = -.52$, $P < .05$), and fine motor (Pearson $r = -.75$, $P < .002$) ability as measured by the McCarthy Scales of Children's Abilities at 4 years of age. When other known predictors of developmental outcome were taken into account by means of multiple linear regression analyses, exclusive formula use emerged as an important predictor of the children's cognitive functioning at 2 years (model $R^2 = .59$, $P < .005$) and of quantitative (model $R^2 = .58$, $P < .006$), perceptual (model $R^2 = .63$, $P < .009$), and fine motor ability (model $R^2 = .74$, $P < .003$) at 4 years of age. These data raise concern about the developmental outcome of the children exposed to chloride-deficient formula. *Pediatrics* 1987;79:851–857; *chloride-deficient formula, child development, infant feeding, malnutrition.*

ABBREVIATIONS. CDC, Centers for Disease Control; GCI, General Cognitive Index; MDI, Mental Development Index; PDI, Psychomotor Development Index.

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During 1978 and 1979, two infant formulas deficient in chloride were marketed by Syntex, Inc, in the United States.[1] It has been calculated that a minimum of 20,000-infant years of these formulas were purchased. Some of the children who ingested these formulas were noted to have a variety of problems including failure to thrive, lethargy, anorexia, and weakness.[2] Severe metabolic derangements including hypochloremia, alkalosis, hypokalemia, hyponatremia, hyperaldosteronism, and elevated plasma renin activity were present in some of these children.[3] The aggregation of these signs, symptoms, and laboratory findings has been termed the chloride depletion syndrome[3] or the dietary chloride deficiency syndrome.[2] Although resolution of these acute problems occurred following the restoration of a diet adequate in chloride,[4] the question of whether or not these children will experience any long-term effects has been raised[5] and remains unanswered. In addition, subsequent to this epidemic of defective formula use, the dietary chloride deficiency syndrome has been reported in a breast-fed infant[6] and in children receiving other defective infant formulas.[7] We studied a group of children who had ingested the defective Syntex formulas and had documented hypochloremic metabolic alkalosis resulting from this ingestion. Twenty-one of these exposed children were developmentally evaluated at 2 years of age and 18 of these returned for reexamination at 4 years of age.

METHODS

Population Studied

The Centers for Disease Control (CDC) in Atlanta, assembled a registry of documented cases of

hypochloremic metabolic alkalosis secondary to chloride-deficient formula ingestion. Reports were obtained from a variety of sources including a survey of pediatric nephrologists, a survey of chairmen of departments of pediatrics, a registry kept by the manufacturers of the defective formula, pediatricians treating children who received the deficient formula, and parents who contacted the CDC. A total of 450 medical records were received from which 121 children were indentified as having ingested one of the defective formulas and as having had documented hypochloremic metabolic alkalosis. From these 121 children in the CDC registry, subjects were recruited for this study by telephoning the parents of these children. They were blindly selected from the registry without reference to length of exposure or outcome information. Because of the limited availability of resources for the careful examination of these children, the study number was limited to 21. Of the first 21 sets of parents who were reached by telephone, 20 agreed to participate (including the parents of one set of identical twins).

Measurements

Each child's mother was interviewed by a psychologist (H.M.) to obtain demographic data as well as information about family structure, formula ingestion, and medical history. Exposure and medical history information was transcribed from tape recordings of these interviews, and this information was abstracted from the transcription by a physician and verified to the extent possible by review of medical records. Exposure information obtained from medical records and interviews was designated as age of onset of defective formula use (age onset), length of time defective formula was used (total use), and length of time defective formula was used when no other nutritional supplementation was ingested (exclusive use). The Bayley Scales of Infant Development were administered to all children at approximately 2 years of age. The Bayley scales are composed of two scales: the Mental Development Index (MDI) assesses a child's cognitive abilities and the Psychomotor Development Index (PDI) assesses a child's body coordination, control, and skill. Each of these two scales results in a raw score which is converted into a standard score having a mean of 100 and an SD of 16.[8]

Approximately 20 months after the initial evaluation, 18 of these children returned for reexamination and the McCarthy Scales of Children's Abilities were administered. This test battery is composed of 18 different tests of a child's cognitive and motor skills. The test scores are grouped to yield six scores: General Cognitive Index (GCI) and Verbal, Perceptual, Quantitative, Memory, and Motor scores. These scores are each composed of a raw score which is converted to a standard score. The GCI has a mean of 100 and an SD of 16, whereas each of the five specific scales has a mean of 50 and an SD of 10.[9] The motor scale is composed of scores of both gross motor and fine motor ability. A fine motor score was derived by adding together the raw scores on the three test items pertaining to fine motor skill.

Statistical Methods

One set of identical twins was enrolled for study. However, to maintain statistical independence of observations, one twin was randomly eliminated from the analyses and the data tables appearing in this report. Initially, Pearson product-moment and Spearman rank-order correlations and their tests of significance were calculated between length of exclusive use and cognitive outcome at 2 (MDI) and 4 (GCI) years of age. Subsequently, these same statistics were computed for all three exposure variables (age onset, total use, exclusive use) and each outcome variable (MDI, PDI, GCI, the five McCarthy scales, and the derived fine motor score). Multiple linear regression analyses were then performed. Each of the nine outcome variables were used as dependent variables. Ten independent variables were identified: age at testing, mother's education, father's education, mother's age at child's birth, child's birth weight, child's sex, birth order, age onset, total use, and exclusive use. The all-possible subsets variable selection procedure was used in conjunction with the Mallows' CP statistic[10] to determine the most predictive subset of independent or predictor variables for the nine dependent variables. This procedure was performed twice, once excluding total use as an independent variable and using all nine others and once removing exclusive use and using all nine other independent variables. All P values were based upon two-sided hypothesis tests. Because the data set had a small number of observations, regression diagnostics were performed to assess whether any particular observations unduly influenced the analyses and results.[11] The Statistical Analysis System[12] and BMDP[13] were used to perform the data analyses.

RESULTS

Birth, demographic, and exposure information are given in Table 1. Eleven girls and nine boys were evaluated. All were full-term births and, with one exception, all weighed more than 2,500 g. Both mothers and fathers were well-educated with no parent having less than a completed high school

education. The exposure variable of exclusive use had a mean of 13.5 weeks, with a range of 0 to 30 weeks. Two children never received deficient formula as their exclusive source of nutrition. Total use ranged from 7 to 35 weeks with a mean of 22.8 weeks.

Scores from developmental testing are provided in Table 2. The mean score on the Bayley MDI and PDI occurs near the standard mean of 100 with a MDI mean of 98.6 and a PDI mean of 103.4. This is also true of the McCarthy GCI and the five individual scale scores. The prenatal, perinatal, and early childhood medical problems were examined for children with long and short exposures to the deficient formula. Long exposure is taken as more than the median number of weeks of exclusive use (15 weeks), whereas short exposure is less. Among the children with long exposure, two had neonatal hyperbilirubinemia and one was an infant of low birth weight. There were two children with ventricular septal defects, one with the Pierre-Robin anomalad, and four with neonatal hyperbilirubinemia in the short-exposure group.

The strong negative correlation that emerged between exclusive use and MDI at 2 years of age (Pearson $r = -.55$, $P = .01$) is shown in Table 3. The negative correlation between the length of exclusive use and the McCarthy GCI obtained at a mean age of 43.8 months is somewhat less strong and does not achieve statistical significance (Pearson $r = -.44$, $P < .09$). Because the correlation between exclusive use and GCI was suggestive of the same negative relationship seen between exclusive use and MDI, further univariate analyses were performed to investigate specific dysfunctional areas that might be related to formula use. When correlations were calculated between length of exclusive use and the five McCarthy subscales and the derived fine motor score, three of these six subscale scores were significantly and inversely cor-

TABLE 1. Study Subjects' Birth, Demographic, and Exposure Information

	Mean ± SD	Range
Birth wt (g)	3,262.9 ± 454.4	1,999–4,025
Mother's age at child's birth (yr)	28.1 ± 5.1	22–38
Mother's education (yr)	14.1 ± 2.2	12–19
Father's education (yr)	14.9 ± 2.4	12–19
Parity	2.4 ± 1.1	1–6
Age of onset of defective formula use (mo)	1.5 ± 1.1	0–4
Length of total use of defective formula (wk)	22.8 ± 7.7	7–35
Length of exclusive use of defective formula (wk)	13.5 ± 9.3	0–30

TABLE 2. Developmental Test Scores and Age at Testing*

Patient No.	Bayley Scales			McCarthy Scales of Children's Abilities						
	MDI	PDI	Age at Testing (mo)	GCI	Verbal	Quantitative	Perceptual	Memory	Motor	Age at Testing (mo)
1	85	107	18	147	78	70	58	77	38	51
2	97	73	13	88	36	50	53	34	45	46
3	85	94	18	†	†	†	†	†	†	†
4	97	73	20	88	45	51	50	43	42	47
5	104	108	21	98	50	41	50	50	45	44
6	67	80	23	†	†	†	†	†	†	†
7	114	131	25	109	56	52	56	52	54	44
8	114	100	21	112	56	53	58	54	51	41
9	97	131	20	111	54	65	50	51	51	41
10	104	†	23	107	49	61	57	51	54	41
11	93	100	21	86	42	40	44	45	44	44
12	70	80	25	‡	‡	‡	‡	‡	‡	‡
13	111	100	25	108	53	48	60	55	55	44
14	72	91	26	76	40	43	32	49	46	45
15	85	116	27	72	34	44	32	43	30	44
16	122	99	28	126	63	69	69	58	62	43
17	127	131	26	96	48	45	45	48	44	42
18	106	125	28	94	44	48	50	42	60	40
19	108	†	28	‡	‡	‡	‡	‡	‡	‡
20	113	123	29	‡	‡	‡	‡	‡	‡	‡
Mean	98.6	103.4	23.2	101.2	49.9	52.0	51.0	50.1	48.1	43.8
SD	17.0	19.6	4.2	19.3	11.1	9.8	9.9	9.6	8.4	2.8

* Abbreviations: MDI, Mental Development Index; PDI, Psychomotor Development Index; GCI, General Cognitive Index.
† Patient uncooperative or ill at time of testing.
‡ Patient did not return for second evaluation.

TABLE 3. Correlation of Length of Exclusive Use With Developmental Outcome

Developmental Outcome Test	No. of Observations	Pearson Product-Moment Correlation		Spearman Rank Correlation	
		r Value	*P* Value	*r* Value	*P* Value
Mental Development Index	20	−.55	.01	−.51	<.02
McCarthy Scales					
General Cognitive Index	15	−.44	<.09	−.43	<.10
Perceptual	15	−.51	<.05	−.67	<.006
Motor	15	−.52	<.05	−.59	<.02
Quantitative	15	−.60	<.05	−.46	<.07
Fine motor	14	−.75	<.002	−.80	<.0005

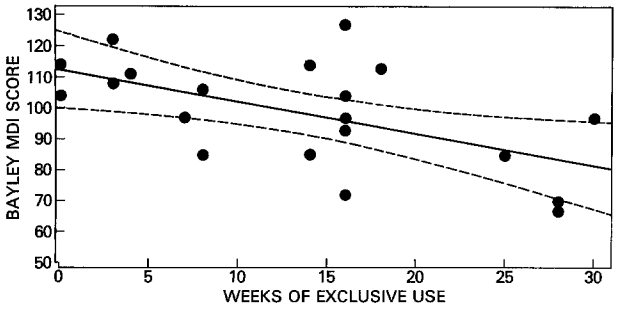

Fig 1. Regression line with 95% confidence limits (for line) between length of exclusive use of defective formula in weeks and score on the Bayley Mental Development Index at 2 years of age.

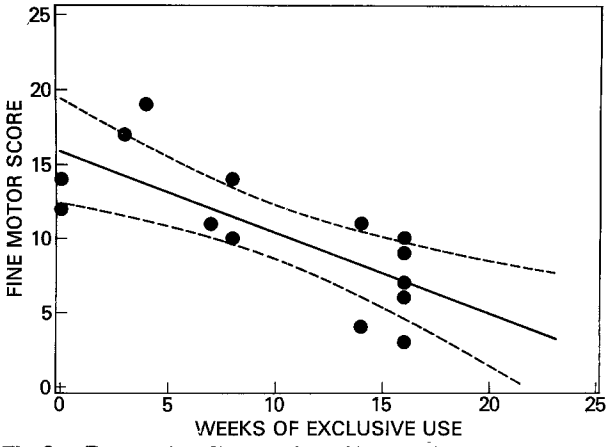

Fig 2. Regression line with 95% confidence limits (for line) between length of exclusive use of defective formula in weeks and fine motor score. One point represents two individuals.

related with the exclusive exposure variable: perceptual score (Pearson $r = -.51$, $P < .05$), motor score (Pearson $r = -.52$, $P < .05$), and fine motor score (Pearson $r = -.75$, $P < .002$) as seen in Table 3.

The regression line with 95% confidence limits of the line for the relationship between length of exclusive use in weeks and score on the Bayley MDI at 2 years of age is shown in Fig 1. The regression line with 95% confidence limits of the line for this same exposure variable and the fine motor score derived by us from the McCarthy motor score is shown in Fig 2.

When multiple linear regression analyses were performed with each of the nine outcome variables used as the dependent variable, exclusive use emerged as an important predictor variable in four of the nine modeling exercises. These results are shown in Table 4. Exclusive use was the most important predictor variable of the MDI and fine motor score. For MDI, the R^2 for the model was .59, $P < .005$. For fine motor score, the model R^2 was .74, $P < .003$. Length of exclusive use contributed .20 and .28 to the R^2 of the models with the MDI and fine motor, respectively, as outcome variables. (Contribution to the R^2 is defined as the amount by which the R^2 would be reduced if that predictor variable was removed from the regression equation.) Length of exclusive use was an important predictor of both the quantitative scale score and the perceptual scale score. In the analysis with the quantitative score as the dependent variable, the model R^2 was .58, $P < .006$, with length of exclusive use contributing .22 to the R^2. Where the perceptual score was the outcome variable, the R^2 equaled .63, $P < .009$. The contribution of length of exclusive use to the R^2 was .16. For each of these four outcome scores, the "best subset" of predictors varied, with only length of exclusive use consistently emerging as an important predictor. Regression diagnostics revealed that no single observation strongly influenced the regression equations.

DISCUSSION

Some of the children who were exposed to a diet deficient in chloride suffered from a constellation of symptoms which has been variously termed the chloride depletion syndrome[3] or the dietary chloride deficiency syndrome.[2] Symptoms included failure to thrive, anorexia, lethargy, and muscle weakness. Laboratory findings included hypochloremia, metabolic alkalosis, hypercalcemia, hypokalemia, hematuria, and elevated levels of renin and aldosterone. After restoration of adequate dietary chloride, even children with severe symptoms and metabolic

TABLE 4. Multiple Regression Analyses With Developmental Outcomes as Dependent Variables

Variable		Regression Coefficient	*P* Value	Contribution to R^2
Dependent	Independent			
Bayley Mental Development Index*	Exclusive use	−.92	.02	.20
	Father's education	−16.37	.03	.17
	Parity	10.71	.08	.10
Fine motor scale†	Exclusive use	−.42	.008	.28
	Test age	.63	.089	.09
	Sex	4.99	.03	.17
Quantitative scale‡	Exclusive use	−.57	.03	.22
	Age onset	−5.7	.004	.44
Perceptual scale§	Exclusive use	−.56	.05	.16
	Mother's age	.99	.02	.26
	Sex	8.22	.06	.14

* Regression 1: R^2 .59, $P < .005$.
† Regression 2: R^2 .74, $P < .003$.
‡ Regression 3: R^2 .58, $P < .006$.
§ Regression 4: R^2 .63, $P < .009$.

derangements demonstrated normal linear growth and weights in the expected range.[14] However, some infants were noted to have delayed motor development during the time of the insult and delay in the acquisition of expressive speech subsequent to the restoration of a normal diet.[15] Although a small number of exposed children were reported to have IQs in the normal range at follow-up of 2 to 5 years,[14] systematic investigation of any long-term effects is lacking.

The generation of hypotheses relevant to this particular exposure proved difficult, given the paucity of descriptions of similar occurrences in the literature. Extrapolation of information from the literature about the developmental sequelae of malnutrition in early childhood is difficult given that starvation often appears in a setting of severe poverty and societal disruption. Some studies attempt to assess the long-term effect of infantile undernutrition on intellectual development by examining children who were malnourished as a result of organic disease. However, these studies demonstrated few statistically significant differences between malnourished and control subjects,[16] have a number of methodologic and reporting difficulties,[17] or have study design deficiencies that limit their usefulness.[18] Studies of conditions that have some metabolic similarity to formula-induced chloride deficiency have shortcomings that make their interpretation difficult[19] or report no statistically significant difference between index and comparison subjects in intelligence testing.[20] It is interesting to note a report of some degree of mental retardation in nine patients with Bartter syndrome (hypochloremic, hypokalemic metabolic alkalosis) who were followed at the National Institutes of Health.[21] There has been some description in the literature of patients with Bartter syndrome suffering from memory deficits, but these studies deal with a small number of patients and neither the methods used for memory testing nor any test results are described.[22,23] Holmberg et al[24] reported that patients with congenital chloride diarrhea and long periods of electrolyte imbalance including hypochloremia and metabolic alkalosis were demonstrated to have retarded mental development, but the mode of assessment and the degree of this retardation is not described in detail.

From the present data, it is impossible to distinguish completely the possible effects of chloride depletion, per se, from the effects of the inanition that accompanied it. However, an assessment of the extent of growth retardation did not appear to relate as clearly to outcome variables as did the length of time of exclusive use of deficient formulas. The data available on growth were gathered from the existing clinical records of these patients and thus were not developed and collected in any standard fashion and were obviously obtained in a variety of conditions, at different times, and using different instruments. Thus, the failure of these measurements to predict outcome may, in fact, relate more to method of collection than to their predictive value.

Because of the difficulty of predicting areas of deficient functioning from previous similar experience, the children evaluated in this study were given a general and broadly based examination of development. Finberg[25] predicted that even minimal nutritional supplementation of the deficient formula with solid foods would protect against problems. Length of exclusive use of formula as well as total length of formula use was carefully quantitated in each maternal interview to investigate the effect of these predictor variables separately. The results demonstrate a clear-cut, dose-response relationship

between the use of this deficient formula without additional nutritional supplementation and deficient cognitive development at 2 years of age. This dose-response relationship persisted at 4 years of age with an inverse relationship between length of exclusive use and cognitive outcome as measured by the McCarthy GCI. Although this latter relationship did not quite reach conventional statistical significance ($P < .05$, two-sided), this may have been due to the fact that several children did not return, including 80% of those in the highest quartile of exposure. Post hoc analysis did demonstrate a significant negative relationship between length of exclusive use and three of the six areas of subscale investigation: quantitative, perceptual, and fine motor abilities.

These data must be viewed with some caution. The number of children evaluated in this study was small. There is almost certainly some selection bias present in the subjects included in this study, because the CDC registry was assembled in both an active and a passive fashion. It is possible that parents who perceived their child as more affected by the formula use or as deficient in functioning from any cause might have been more vigorous in seeing that their child was reported to the CDC. Physicians and departmental chairmen may have been more likely to remember and report when questioned the details of a particularly ill or deficient child than a less affected child. Parents may have been more willing to consent to study participation if they perceived their child to be dysfunctional. It is also possible that children who stayed on the formula longer were children who had prenatal, perinatal, or early neonatal difficulties that placed them at risk for developmental delay unrelated to formula use. There was no control group of children examined as a part of this study. Finally, the only hypothesis generated prior to data analysis was that there would be an association between exclusive use of deficient formula and deficient general cognitive abilities. A significant relationship was demonstrated at 2 but not 4 years. All further analyses of nine dependent and ten independent variables must be subject to a criticism of both multiple comparisons and post hoc hypotheses generation.

However, despite the small study group, several relationships reported between exposure and outcome were statistically significant. Selection bias may have operated in a fashion opposite to that described before, because parents reporting their children to the CDC may have been parents who were vigorous in acting as their child's advocate and thus likely to provide especially nurturing homes. Thus, the CDC registry is as likely to represent an advantaged population as a particularly badly affected one. Also, pediatric nephrologists and departmental chairmen were polled concerning all cases of formula-induced hypochloremic metabolic alkalosis prior to the time that any children were reported as cognitively disabled secondary to formula use. Given that such cases were a relatively rare occurrence, selective recall by the medical personnel involved is unlikely. As to selective participation on the part of parents, there was only one refusal from the group of parents invited to participate. Children were selected for invitation to participate from the CDC registry without any reference to outcome problems. When children who had less exposure to the formula were compared with those with a higher exposure the prevalence of prenatal, perinatal, and early childhood problems was higher in the low compared with the high exposure group, suggesting that children with preexisting problems were less numerous in the high exposure group. This increases the likelihood that deficits are indeed related to formula use rather than some other cause. With reference to the problems posed by the lack of a control group, it is difficult to postulate a selection or reporting bias that could produce the marked and clear-cut dose-response relationships demonstrated in this paper. Finally, with regard to the multiple comparisons and post hoc hypotheses generation problem, the relationships demonstrated between formula use and specific areas of dysfunction may simply be regarded as areas for future investigation.

SUMMARY

Although the study deficiencies cited are of concern, a dose-response relationship has been demonstrated in a group of children with a wide range of deficient formula exposure. A larger group of children with appropriate controls should be examined at an age when developmental testing is more reliable and valid. Nevertheless, these data raise considerable concern about the outcome of children exposed to a chloride-deficient formula. Until further data are available, exposed children should be considered at risk for developmental dysfunction.

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ALCOHOL AND DRUG ABUSE AMONG ADOLESCENTS

Motor vehicle accidents involving alcohol are the leading cause of death for young Americans aged 15 to 19, accounting for 45% of fatalities in this age group.

Source: Vital Statistics in the US, 1980, vol II, Mortality, part A. US Department of Health and Human Services, 1985, as quoted in *ADAMHA Update*, April 1986.