

Perinatal Factors Associated With Epilepsy in Negro Children

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SINCE 1951 a number of retrospective studies have reported positive associations of certain neurological and psychological disorders in children with maternal complications of pregnancy and delivery and with prematurity (1-12). On the basis of these findings it has been asserted that there exists a continuum of reproductive casualty composed of a lethal and a sublethal component. The former consists of abortions, stillbirths, and neonatal deaths. The latter consists of cerebral palsy, epilepsy, mental deficiency, behavioral disorders, reading disabilities, and, possibly, tics in children. Another condition studied, childhood speech disorders, was not found to be associated with abnormalities of pregnancy and delivery or with prematurity (13).

This series of studies stimulated interest in the perinatal period and its possible etiological role in many diseases. Yet no attempt seems to have been made to repeat any of the studies. This paper is, in part, such an attempt and relates to the study on epilepsy (2) first reported by Lilienfeld and Pasamanick in 1954. That study was chosen because it was fairly

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typical of the series, could be repeated for approximately the same geographic area, and had certain inconclusive results which seemed to warrant further investigation.

Lilienfeld and Pasamanick selected as their epilepsy case group all patients with epilepsy diagnosed in a number of clinics and institutions in Baltimore who were born in the city during the period 1935 through 1952. Using the birth register of the Baltimore City Health Department, a control group was chosen by taking the next birth reported from the same place of birth as the epilepsy case, matched by race and maternal age group. If the matched control had died during the neonatal period, this birth was omitted and the next birth with the matching characteristics was selected as the appropriate control.

A total of 274 white epileptics and 122 non-white epileptics were finally studied. These children were single hospital births, and information about pregnancy and delivery was abstracted from the hospital records.

The authors found significantly more complications of pregnancy and delivery, more prematurity, and more abnormal neonatal conditions associated with epilepsy in the white case group than with their matched controls; for nonwhites, differences observed were not statistically significant for complications of pregnancy and delivery nor for prematurity, although in the same direction as found among whites. The authors comment that "one possible reason for this may be that the size of the nonwhite group is too small to be able to detect a difference." However, significantly more abnormal neonatal conditions were noted

among nonwhite cases than among their matched controls. The association between epilepsy and perinatal disorders in white children was positive for low birth weight and for those medical complications of pregnancy thought to produce chronic infant anoxia; that is, the toxemias and the various types of bleeding.

Neither that study nor the others previously mentioned showed significant associations with such complications of delivery as dystocia and pelvic abnormalities which are in turn related to mechanical injury.

Another positive finding was that mothers of epileptics had a history of previous infant loss more often than the mothers of controls (5, 6).

The authors also studied duration of labor and the types of operative procedures performed at delivery, and they noted no essential differences between case and control groups in either race.

Objectives and Study Design

The main objectives of the present study were to determine (a) whether Negro children with epilepsy are characterized by low birth weight, and (b) whether the pregnancies of mothers of Negro children with epilepsy are characterized by an excess of selected perinatal disorders. Names of children with epilepsy were obtained from the files of the epileptic clinics of the University of Maryland and Johns Hopkins Hospitals or from one of their subsidiary units in the counties of Maryland and from the handicapped and crippled children's service of maternal and child health, D.C. General Hospital, Washington, D.C.

For the purposes of this study, epilepsy was defined as a chronic recurrent disorder of the state of consciousness, and two or more seizures were required before the diagnosis was accepted. Cases diagnosed as epilepsy by neurologists in one of the clinics and meeting these two criteria were included in the study. No attempt was made by any observer in this study to make a diagnosis from hospital records.

Case selection was confined to Negro children born in hospitals in Maryland or the District of Columbia since January 1, 1950, and diagnosed before April 1, 1962. Only single births were

considered, and selection was restricted to out-patient clinics so that epilepsy would tend to be the major diagnosis.

At the outset, 447 names of children with epilepsy who were single live births were obtained. Records of births were not available for 118 born at home or enroute to the hospital and 30 born in hospitals. These 148 were excluded from the study, leaving a total of 299 which comprised the case group. One hundred and eighty-three of these children were born in Baltimore, 56 in the rest of Maryland, and 60 in the District of Columbia. In the excluded group, 74 were born in Baltimore, 54 in the rest of Maryland, and 20 in the District of Columbia.

The majority of those in the case group were born in Baltimore. Initial planning indicated that at least 300 children born in Maryland since 1950 could be obtained for study. Since only 239 qualified, it was considered necessary to add cases from another source, the District of Columbia. This accounts in part for inclusion in the study of a much smaller number born in the District of Columbia. There were more males than females in the case group; the male-to-female ratio was about 1.5 to 1. A similar sex ratio was observed in the excluded group.

Of the 299 children, 219, or 73 percent, were born in 1 of the 5 hospitals listed. Following are the hospitals of birth for those in the case group.

<i>Hospital</i>	<i>Number</i>	<i>Percent</i>
University	42	14.0
Johns Hopkins.....	46	15.4
Baltimore city.....	65	21.7
Providence.....	26	8.7
Other hospitals in Baltimore city....	4	1.3
Maryland hospitals outside of Baltimore city.....	56	18.7
District of Columbia General.....	40	13.4
Other District of Columbia hospitals..	20	6.7
Total.....	299	100.0

The age distribution for mothers of children with epilepsy was compared with a percent distribution for mothers of all Negro live births in Maryland and the District of Columbia in 1955 (table 1). There were only minor differences between the two distributions.

Table 1. Age of mothers of epileptic children and of Negro mothers, all live births in Maryland and the District of Columbia in 1955

Maternal age (years)	Case group		All Negro live births ¹ (percent)
	Number	Percent	
Under 15.....	4	1.3	0.9
15-19.....	58	19.4	20.0
20-24.....	82	27.4	31.8
25-29.....	75	25.1	23.7
30-34.....	46	15.4	15.0
35-39.....	23	7.7	6.9
40 or more.....	11	3.7	1.6
Total.....	299	100.0	100.0

¹ SOURCE: National Office of Vital Statistics, Vital Statistics of the United States, 1955, Vol. 1. U.S. Government Printing Office, Washington, D.C.

The type of epilepsy and reported presence of other significant diagnoses (cerebral palsy and mental retardation only) are shown by sex in table 2. The most frequent type of epilepsy for each sex was grand mal, with relatively few cases reported with other types. Of the 299 children, 16, or about 5 percent, were known to have cerebral palsy or mental retardation and for this reason were excluded from further analysis. This left a total of 283 children with epilepsy (but without cerebral palsy or mental retardation at the time of the diagnosis of epilepsy) as the case group finally studied.

Two control groups designed to meet the two study objectives were used. Control group A was chosen by matching with the case group in respect to date of birth, hospital of birth, plurality, sex, maternal age, and birth weight. Categories for maternal age were under 20 years, 20-34 years, and 35 years or more. Categories for birth weight, in grams, were under 2,001, 2,001-2,500, 2,501-4,000, and 4,001 or more. Birth certificates on file at the Baltimore City, State of Maryland, and District of Columbia vital statistics offices were used to obtain matches for each epilepsy case. The procedure was to choose the next birth certificate number which represented a Negro of the same sex, plurality, birth weight, and maternal age categories and who was also born in the same hospital as the child with epilepsy. This control group included those surviving the 28-day

neonatal period and replacements for those who died in the neonatal period. Each replacement was the next child with matching characteristics who survived the neonatal period.

Control group B was chosen in the same way as control group A but without matching for birth weight. For control group B, birth weight was obtained directly from the birth certificate. No further information except that needed for matching purposes was obtained, since this group was intended solely for comparison of birth weight with the case group.

For the epilepsy cases and for control group A, obstetrical information concerning the pregnancy was obtained from the hospital records. Care was taken to insure that the medical students abstracting this information would be unaware of whether the birth was of an epileptic or of a control child. An instruction manual was prepared to describe the process of abstraction and to give definitions used in this study. (See box, p. 504.)

Results

Results relate only to those 283 of the original 299 children who had neither cerebral palsy nor mental retardation at the time of diagnosis of epilepsy.

The birth weights of the case group of children were compared with the birth weights of

Table 2. Type of epilepsy and reported presence of other significant diagnoses, by sex, for the case group

Type of epilepsy	No other significant diagnoses		Other significant diagnoses ¹	
	Male	Female	Male	Female
Grand mal.....	124	82	7	8
Petit mal.....	9	6	0	0
Temporal lobe or psychomotor.....	1	0	0	0
Focal (sensory or motor).....	10	5	0	0
Grand mal and petit mal.....	1	0	0	0
Grand mal and focal.....	4	2	0	0
Petit mal and focal.....	0	1	0	0
Unknown.....	23	15	0	1
Total.....	172	111	7	9

¹ Includes cerebral palsy and mental retardation.

Summary of Instructions to Abstracters

Both outpatient and inpatient records must be used. Information about the prenatal period must be taken from the prenatal chart and not from an historical summary recorded at the time of admission for delivery.

Previous pregnancies include all pregnancies prior to the study pregnancy.

An affirmative diagnosis of toxemia, preeclampsia, eclampsia, or hypertension without eclampsia can only be accepted if stated categorically to be present by an obstetrician.

Hyperemesis, threatened abortion, or unclassified vaginal hemorrhage can only be accepted if the patient was hospitalized for treatment of the condition.

Urinary tract infection can only be accepted if there is a history of treatment of infection during the study pregnancy.

All abnormal or pathological conditions of the placenta must be described.

An abnormality of the bony pelvis, an abnormality of the birth canal, a retained or adherent placenta can only be accepted if described by the obstetrician. Details of the described abnormality should be abstracted in full.

If any anatomical, physiological, or medical condition or process was described by the obstetrician as normal, no complication or abnormality is considered to be present. If the anatomical, physiological, or medical process is not described by the obstetrician as normal and no complication is described, the presence of a complication or abnormality is considered to be unknown.

Hypertension, heart disease, diabetes, or any other medical condition can only be stated to be present if categorically described by the obstetrician or attending physician.

No diagnosis can be made by the abstractor on the basis of symptoms.

control group B. These results and a cross-classification of birth weights for cases and controls are presented in table 3. The number of infants in the case group weighing more than their matched controls was about the same as the number weighing less than their matches. On the average, infants with epilepsy weighed about 36 grams less than their matches, a differ-

ence far too small to be statistically significant.

(The 0.05 level is used for statistical significance in this paper.)

A somewhat greater number of prematures (weight of 2,500 grams or less) was observed for cases than controls—38 compared with 28. However, this difference was not statistically significant. Further, these data indicate little

Table 3. Birth weight, in grams, of case group and control group B

Weights of case group	Matched controls B									Total
	Less than 1,001	1,001-1,500	1,501-2,000	2,001-2,500	2,501-3,000	3,001-3,500	3,501-4,000	4,001-4,500	4,501-5,000	
Less than 1,001							1			1
1,001-1,500				1	4	2	2			9
1,501-2,000					1	4	2			7
2,001-2,500				2	3	10	5	1		21
2,501-3,000			1	7	16	30	14	4		72
3,001-3,500		1	3	8	26	47	14	2		101
3,501-4,000			1	2	16	20	11	3	2	55
4,001-4,500	1	1			2	5	1	1		11
4,501-5,000					1	2	3			6
Total	1	2	5	20	69	120	53	11	2	283

NOTE: 138 epileptic children weighed more than their matched controls, 143 weighed less, and 2 weighed exactly the same. Average weight difference: case to control = -36.1 grams.

Table 4. Complications of labor and of pregnancy prior to hospitalization

Complication	Pregnancy		Labor	
	Cases	Controls	Cases	Controls
<i>Pregnancy</i>				
Unclassified vaginal hemorrhage.....	7	2		
Hyperemesis.....	1	2		
Renal disease.....	1	0		
Threatened abortion.....	1	2		
<i>Labor</i>				
Abnormality of bony pelvis.....			15	8
Premature separation of placenta.....			6	7
Retained or adherent placenta.....			5	2
Abnormality of birth canal.....			3	1
Prolapsed cord.....			3	1
Other antepartum hemorrhage.....			1	1
Placenta praevia.....			0	1
<i>Pregnancy and Labor</i>				
Hypertension without eclampsia.....	13	13	13	11
Preeclampsia.....	11	19	15	18
Urinary infection.....	7	5	2	1
Heart disease.....	5	2	4	2
Toxemia.....	3	2	2	0
Epilepsy.....	2	0	1	0
Diabetes.....	1	2	1	2
Eclampsia.....	0	2	1	1
Other ¹	40	37	42	47
Total with 1 or more.....	71	70	90	85
Total without complications.....	171	174	188	196
Total without information.....	41	39	5	2
Total in study.....	283	283	283	283

¹ Includes a variety of symptoms and minor disorders. Most frequent for pregnancy were edema, obesity, and cervicitis. Most frequent for labor were premature rupture of membranes, lacerations, and uterine inertia.

if any essential difference in the birth weight distribution between case and control groups.

Table 4 summarizes data on specific complications of pregnancy before hospitalization and complications of labor after hospital admission. Generally, no substantial differences were noted between mothers of children in the case group and those of the control children. However, 15 of the mothers of the case group had an abnormality of the bony pelvis, compared with 8 mothers of controls. This fact is reflected in the greater number of cesarean sections among mothers of epileptic children.

As a further check to see if differences between case and control groups had been obscured by inclusion of unimportant complications, the following analyses were carried out. All medical complications of pregnancy or delivery or both were listed for each woman, and she was assigned to the class of the most

important complication according to the following order of preference: (a) hemorrhage; (b) toxemia, preeclampsia, or eclampsia; (c) hypertension; (d) urinary tract infection; and (e) hyperemesis.

Also, all mechanical complications of delivery were listed for each woman, and she was assigned to the class of the most important complication. The order of preference of major mechanical complications was (a) disproportion or contracted pelvis, (b) breech, (c) dystocia, (d) uterine inertia, and (e) prolapsed cord.

A total of 75 mothers of epileptic children had one or more major medical or mechanical complications as compared with 70 mothers of control children (table 5). For major medical complications, little difference between mothers of the two groups was noted, but 37 mothers of those in the case group had major mechani-

cal complications, compared with 23 mothers of controls. This difference, however, was not quite statistically significant ($P=0.056$). (Fisher's exact test is used here and elsewhere in this paper. The probability indicated by P is the chance probability of obtaining a difference as rare or rarer than that observed.) The observed difference is largely due to the categories "disproportion or contracted pelvis" and "dystocia."

The length of labor was similar for mothers of the case and control group children, but this information was not reported in about 16 percent of the records. For vaginal deliveries, there were no appreciable differences in presentation at delivery.

The type of delivery and operative procedures used follow.

Type of delivery	Cases	Controls
Without assistance.....	194	211
Cesarean section.....	18	8
Manual rotation.....	1	5
Low forceps.....	55	49
Mid forceps.....	4	3
High forceps.....	0	1
Forceps, type unknown.....	1	5
Manual rotation and forceps....	3	0
Unknown.....	7	1
Total.....	283	283

No striking differences were noted between cases and controls, although a greater number of cesarean sections were observed for the case group, 18, compared with 8 for the control group. This difference was statistically significant at the 5 percent probability level ($P=0.045$).

About 30 percent of case group mothers with one or more previous pregnancies had at least one previous pregnancy loss (abortion or stillbirth); the comparable figure for mothers of the controls was 21 percent (table 6). For three of the five categories listed, a somewhat greater proportion of the case group mothers than of the controls had at least one previous pregnancy loss. The overall difference noted was statistically significant at the 5 percent probability level ($P=0.048$).

Information was collected on month of pregnancy at which the first clinic or office visit was made. However, for about a third of the

records these data were not available. For those with available information—182 cases and 178 controls—only slight differences were observed between cases and controls. There were 33 mothers of epileptic children with no prenatal visit compared with 31 among the controls. Of the remaining 149 case group mothers, there were 22 with first visits in the first trimester, 74 in the second trimester, and 53 in the third trimester. For the remaining 147 controls, the comparable numbers were 16 in the first trimester, 84 in the second, and 47 in the third.

Length of gestation was also recorded for those in the case and control groups. This was measured from the first day of the last normal menstrual period (LMP) to the date of birth. Since the children in the case group and control group A were matched for birth weight, which is known to be directly associated with length of gestation, little difference in gestation was anticipated between cases and controls. The

Table 5. Major medical and mechanical complications of pregnancy and delivery

Complications	Number	
	Cases	Controls
Major medical complications ¹	50	53
Hemorrhage (early and late).....	11	13
Toxemia, preeclampsia or eclampsia.....	22	24
Hypertension.....	11	11
Urinary tract infection.....	5	3
Hyperemesis.....	1	2
Major mechanical complications ²	37	23
Disproportion or contracted pelvis.....	20	12
Breech.....	7	6
Dystocia.....	5	0
Uterine inertia.....	3	4
Prolapsed cord.....	2	1
Major medical or mechanical complications:		
Total with 1 or more.....	75	70
Total without complications.....	165	174
Total without information.....	43	39
Total in study.....	283	283

¹ Each patient classified by the single most significant medical complication recorded. Preferential order of classification: (a) hemorrhage; (b) toxemia, preeclampsia or eclampsia; (c) hypertension; (d) urinary tract infection; and (e) hyperemesis.

² Each patient classified by the single most significant mechanical complication recorded. Preferential order of classification: (a) disproportion or contracted pelvis; (b) breech; (c) dystocia; (d) uterine inertia; and (e) prolapsed cord.

Table 6. Previous pregnancy loss, by number of previous pregnancies

Number of previous pregnancies for groups	Number of previous unsuccessful pregnancies ¹								Percent ²	
	Total	0	1	2	3	4	5	Un-known	0	1 or more
One pregnancy:										
Case.....	71	56	15	0	0	0	0	0	78.9	21.1
Control.....	57	50	7	0	0	0	0	0	87.7	12.3
Two pregnancies:										
Case.....	26	21	4	0	0	0	0	1	84.0	16.0
Control.....	54	43	8	1	0	0	0	2	82.7	17.3
Three pregnancies:										
Case.....	37	28	7	1	1	0	0	0	75.7	24.3
Control.....	30	26	1	1	0	0	0	2	92.9	7.1
Four pregnancies:										
Case.....	30	19	7	1	1	2	0	0	63.3	36.7
Control.....	27	17	9	1	0	0	0	0	63.0	37.0
Five or more pregnancies:										
Case.....	57	29	16	8	2	0	1	1	51.8	48.2
Control.....	51	33	10	6	2	0	0	0	64.7	35.3
Total with one or more pregnancies:										
Case.....	221	153	49	10	4	2	1	2	69.9	30.1
Control.....	219	169	35	9	2	0	0	4	78.6	21.4

¹ Includes abortion or stillbirth.

² Percent based on total with known pregnancy outcomes.

differences, as shown in the following data, were relatively small.

Weeks from LMP to date of birth	Cases	Controls
Less than 20.....	1	0
20-27.....	2	8
28-31.....	11	11
32-35.....	26	31
36-40.....	154	156
41 or more.....	56	47
Unknown.....	33	30
Total.....	283	283

The interval from the most recent viable delivery to LMP for cases was compared to that for controls. No consistent differences were observed, but this information was not available on many records (unknown for 54 cases and 57 controls).

Other prenatal information such as the Rh factor, serologic test for syphilis, and hematocrit and hemoglobin values were obtained if available, but only trivial differences were noted between case and control groups. However, about half of the records did not report prenatal hematocrit or hemoglobin measurements, and about a fourth did not report Rh data.

Information was collected on a number of additional factors, including use of vasopressor drugs before or after delivery, blood transfusion, complete or incomplete placental delivery, placental anomalies, and hematocrit and hemoglobin values at delivery. No major differences between the case and control groups were found.

Analgesic and anesthesia drugs were analyzed individually and by appropriate groupings. No appreciable differences were found between case and control groups in the doses of these agents the mothers had received. Information was also collected on post partum complications,

Table 7. Respiratory and neurological abnormalities of infants during nursery period

Abnormality	Cases	Controls
None reported.....	256	266
Respiratory condition ¹	18	16
Neurological condition ²	3	1
Neurological and respiratory conditions.....	6	0
Total.....	283	283

¹ Most frequently noted were anoxia, asphyxia, atelectasis, and respiratory distress.

² Most frequently noted were convulsions and spastic or flaccid extremities.

but no appreciable differences between cases and controls were observed.

The number of significant respiratory and neurological abnormalities of the infants during the nursery period were recorded (table 7). The most frequent diagnoses in the respiratory group were anoxia, asphyxia, atelectasis, and respiratory distress. The most frequent diagnoses in the neurological group were convulsions and spastic or flaccid extremities. More case group infants than controls—27 compared with 17—were reported with such abnormalities during the first days of life. This observed difference, however, was not statistically significant. Twelve of the 27 abnormal case children and 8 of the 17 abnormal control children were born to mothers with no recorded complication of pregnancy or delivery.

<i>Mother's status</i>	<i>Cases</i>	<i>Controls</i>
No complication.....	12	8
Medical complication.....	8	4
Mechanical complication.....	4	4
Medical and mechanical complications.....	3	1
Total.....	27	17

Discussion

The findings of this investigation were negative with respect to both study objectives. Mothers of Negro children with epilepsy did not have an excess of selected perinatal disorders, and the children themselves were not characterized by low birth weight. There are two possible exceptions to the overall negative observations. These are the frequency of cesarean sections and the past history of pregnancy loss.

The results of this study appear to agree in the main with results reported by Lilienfeld and Pasamanick for their nonwhite cases, although interpretations and conclusions differ. The previous investigators found no essential differences between nonwhite cases and their controls for complications of pregnancy, duration of labor, operative procedures, and birth weight. With the possible exception of operative procedures, these are all in accord with present findings. Lilienfeld and Pasamanick

attributed the lack of significant differences between cases and controls in their nonwhite group to insufficient numbers. Another possibility they suggested was that postnatal causes of epilepsy may have been more common among the nonwhites studied than among the whites, thereby diluting case-control differences in the nonwhite group. However, with an appreciably greater number of cases, the present study not only fails to achieve significance but generally fails to demonstrate any consistent direction of differences between cases and controls. In addition, this study has failed to show any association between epilepsy and other relevant perinatal variables not previously studied.

If there is in fact a "continuum of reproductive casualty," there is little evidence from the present study that epilepsy in Negro children is a component of such a "continuum." An obvious question remains to be answered: would a similar study of white epileptic children support the evidence of Lilienfeld and Pasamanick (2) that epilepsy in white children is associated with perinatal complications. If it did, we are faced with a difference in associations between Negro and white epileptic children. Such a difference could be the result of initial selection for attendance at epilepsy clinics, or it could be the result of a different relative distribution of types of epilepsy among Negro and white children. If a similar study on white epileptic children did not support previous observations, then questions have to be answered about selection factors in identification of children in both studies.

Summary

A total of 299 Negro epileptic children born since 1950 in Maryland or Washington, D.C., were studied retrospectively. Each index case was matched, from birth certificates, with a control case for race, sex, plurality, birth weight, hospital of delivery, age of mother, and date of delivery. Children with diagnoses of mental retardation or cerebral palsy were eliminated from the case group.

Review of the hospital prenatal and delivery records showed that the pregnancies of the 283 mothers of children in the case group were similar to that of mothers of the control group in

the frequency of hemorrhagic, toxemic, and other medical complications. Although not statistically significant, the mothers of epileptic children had more mechanical complications of delivery. A somewhat greater proportion of mothers of the case children than mothers of controls had at least one previous pregnancy loss (abortion or stillbirth), and a greater proportion of the epileptic children were delivered by cesarean section.

In addition, comparison with a second matched group showed that children with epilepsy were not characterized by low birth weight.

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