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Etiologic Yield of Cerebral Palsy: A Contemporary Case Series

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Cerebral palsy is an established symptom complex that results from heterogeneous etiologies. Our understanding of the relative contribution of underlying etiologies to the occurrence of cerebral palsy is largely derived from studies lacking systematic neurologic evaluation or the application of contemporary imaging modalities. Throughout a 10-year inclusive period, the case records of all consecutive patients diagnosed with cerebral palsy in a single pediatric neurology practice were reviewed with reference to clinical features and diagnostic yield. A total of 217 cases of cerebral palsy were identified (129 male, 88 female): 77 (35.5%) spastic quadriplegic, 68 (31.3%) spastic hemiplegic, 39 (18%) spastic diplegic, five (2.7%) spastic monoplegic, 12 (5.5%) mixed, 12 (5.5%) ataxic-hypotonic, two (0.9%) dyskinetic, two (0.9%) Worster-Drought syndrome. Overall etiologic yield was 82.0%, varying according to type of cerebral palsy: 50% dyskinetic, 59% diplegia, 80% monoplegia, 80.9% hemiplegia, 90.9% quadriplegia, 91.7% ataxic hypotonia, and 100% mixed/Woster-Drought. The top five etiologic entities identified were periventricular leukomalacia, 24.9%; intrapartum asphyxia, 21.7%; cerebral dysgenesis, 17.1%; intracranial hemorrhage, 12.9%; and vascular, 9.7%. Although a single etiology was apparent in 144 (66.4%) of the cases, multiple etiologies were believed to be contributory in 34 (15.6%) of the cases. The etiologic profile varied according to such features as the type of cerebral palsy, gestational age, and the source (high-risk neonatal population or not) of the patients. Features of the child's cerebral palsy, such as microcephaly, neonatal difficulties, prior or coexisting epilepsy, and high-risk source, were found to be predictive of eventual etiologic yield. This contemporary evaluation of cerebral palsy etiologic yield suggests that it is much higher than previously reported and varies, depending on key clinical features.

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Introduction

Cerebral palsy is a "term of convenience" first introduced into medicine in the latter part of the nineteenth century [1]. Consensus agreement regarding the precise meaning of this term has often been elusive. Presently, it is best considered a clinically defined symptom complex that is applied to individuals with a static, nonprogressive motor impairment of early onset that is cerebral in origin [2]. It is thus not a single entity with respect to pathogenesis but rather is etiologically heterogeneous with multiple possible causes that feature either an aberration or injury to the maturing central nervous system [3]. The prevalence of cerebral palsy is estimated between 1.5 and 2.5 per 1,000 live births [2,4], and there is a considerable burden (personal, familial, and societal) attached to its associated lifelong disabilities [5].

Recent clinical research in cerebral palsy has focused on the identification of prenatal or perinatal risk factors for later cerebral palsy [6-8]. This effort has contributed to the attempt to identify possible pathogenic mechanisms. Additionally, efforts have concentrated on the establishment and maintenance of cerebral palsy registries to compare the prevalence of cerebral palsy throughout geographic locales and time and to better delineate its demographic profile [9].

Despite these efforts, uncertainty continues to exist regarding the spectrum of etiologies and their relative contribution in a population-derived sample of individuals with this etiologically heterogeneous disorder. Historically, the role of intrapartum asphyxia has been emphasized [10-12] and has had considerable obstetric interventional and medical-legal implications [13]. Controversy exists regarding the precise frequency of intrapartum

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asphyxia as a cause of cerebral palsy and the frequency of cerebral palsy without apparent cause. Technologic advances (especially imaging) and their systematic clinical application have certainly influenced the identification of possible causes and reduced the portion of cerebral palsy that is of unknown cause [11]. Additionally, imaging has contributed to the increasing recognition that developmental malformations of the brain are a frequently documented cause of cerebral palsy [14]. Knowledge of the causes of cerebral palsy, including their distribution and relative frequency, will have significant implications for ongoing efforts directed at intervention and prevention strategies.

The objective of our study was to identify the causes of cerebral palsy and their relative frequency in a contemporary consecutive series of community-derived patients with this symptom complex evaluated by a single pediatric neurologist throughout a 10-year interval (1991-2001). A rigorous consistent definition for cerebral palsy was used, reflecting our contemporary understanding of this entity. Similarly, a precise stringent definition for the identification of intrapartum asphyxia as a potential cause was applied. Each patient underwent a detailed neurologic evaluation (including computed tomography [CT] or magnetic resonance imaging [MRI] studies) that emphasized the identification of a possible cause for the child's cerebral palsy. The spectrum of causes identified and their relative frequency are reported as a function of the type of cerebral palsy identified and other key demographic features (sex, gestational age, source of patient recruitment). Additionally, features evident on initial evaluation or physical examination that may predict eventual successful diagnostic determination were analyzed and identified.

Methods

Patients for this study were drawn from a comprehensive computerized database of a single university-based pediatric neurologist (M.I.S.). This relational database modified from Microsoft Access contains demographic, clinical, diagnostic, and treatment information (14 fields in all) on all patients treated by this neurologist throughout a 10-year inclusive interval (July 1991-June 2001). Information is entered into this database by the neurologist at the initial patient evaluation and updated as necessary at each subsequent visit according to clinical evolution and the results of diagnostic testing. Patients whose information is entered into this database have been treated by the neurologist in four locales; (1) hospital-based neurology ambulatory clinic with resident house staff, (2) hospital-based private office (1991-1996), (3) hospital-based neonatal neurology clinic for at-risk neonatal intensive care unit survivors, and (4) suburban private pediatric clinic. The majority of patients treated outside of the neonatal neurology clinic were referred for suspected motor impairment, developmental delay, seizures, or early handedness.

The database was systematically scanned (i.e., each computer record reviewed) by the neurologist for all patients with a potential for diagnosis of cerebral palsy (see definition below). The medical files for all such potential patients were retrieved and systematically reviewed for ascertainment of the appropriateness of the cerebral palsy label as defined below. If indeed the diagnosis of cerebral palsy was validated, the patient was included in this study. The relevant medical files were then retrospectively reviewed for identification of (1) specific type of cerebral palsy, (2) clinical features evident at intake (i.e., initial neurologic assessment) to include sex, gestational age, history of neonatal difficulties, presence of microcephaly and coexisting or prior epilepsy, and (3) etiologic determination (if any).

For the purposes of this study, cerebral palsy was defined as a clinically determined symptom complex featuring a static, nonprogressive motor impairment of early onset of presumed cerebral origin. Operationally, the term *static, nonprogressive* meant that although the clinical manifestations of the disorder may change against the backdrop of a maturing central nervous system, the process responsible for the cerebral palsy condition could not be ongoing, that is, inflicting additional brain injury over time. Thus, neurodegenerative, neoplastic, or metabolic processes were excluded. *Motor impairment* referred to objective abnormalities in tone, posture, development, or reflexes documented on examination. *Early onset* referred to symptomatic presentation (e.g., parental concern, early handedness, etc.) but not necessarily evaluation or diagnosis before 12 months of age. *Cerebral origin* eliminates from consideration entities such as neural tube defects and neuromuscular disorders as causes of cerebral palsy. Additionally, disorders not traditionally considered cerebral palsy were excluded according to Badawi et al. [9].

Patients meeting these criteria for diagnosis of cerebral palsy were classified according to type of cerebral palsy, which was based on the predominant pattern of motor abnormalities observed by using the following well-established schema [15,16]: (1) spastic-quadriplegic (equivalent or greater spasticity in upper extremities), hemiplegic, diplegic (spasticity in lower extremities far in excess of any discernible in upper extremities), or monoplegic; (2) dyskinetic; (3) ataxic-hypotonic; (4) Worster-Drought syndrome; or (5) mixed (e.g., spastic and dyskinetic).

Clinical features documented at intake were categorized as follows: (1) gestational age (term, $\geq$ 37 weeks; preterm, $<$ 37 weeks), (2) head circumference (microcephaly $>$ 2 S.D. below the age-adjusted mean for sex), (3) epilepsy (prior documented or coexisting afebrile seizure disorder requiring treatment with antiepileptic drugs), and (4) neonatal difficulties (documentation of encephalopathy, intubation, or intervention [beyond observation] in a neonatal intensive care unit).

Broad categories of possible etiologies were used. The diagnosis of intrapartum asphyxia required the documentation of a moderate to severe neonatal encephalopathy as defined by Sarnat and Sarnat [17] (an essential criterion) with at least three of the following variables: (1) proximate cause (i.e., abruptio, cord prolapse, or maternal hypotension), (2) thick meconium staining, (3) fetal decelerations (prolonged and late), (4) Apgar scores less than 6 at 5 minutes, (5) initial acidosis (pH $<$ 7.0 or base excess $>$ 15), (6) multi-organ involvement, and (7) electrophysiologic/imaging changes consistent with prior asphyxial injury. This approach is generally consistent with the recent British Medical Journal consensus statement on the topic [18]. The diagnosis of periventricular leukomalacia required imaging (CT or MRI, not merely cranial ultrasound) documentation of such changes. Likewise, the categories of intracranial hemorrhage (epidural, subdural, intracranial, and all grades of intraventricular), cerebral dysgenesis, or cerebral atrophy required an imaging finding (CT or MRI) to support such a diagnosis. A vascular etiology was diagnosed when imaging findings revealed a lesion (e.g., porencephaly) in an established vascular territory or distribution consistent with observed physical findings. An infectious etiology required objective cerebrospinal fluid finding or immunologic evidence of intra-uterine infection. Trauma was diagnosed as an etiology based on historic evidence with supportive acute imaging changes. Toxins were diagnosed on historical grounds with either associated dysmorphology (fetal alcohol syndrome) or positive laboratory testing (cocaine, kernicterus).

If more than one of the above etiologic categories was found to be evident or operative in a single case, all such etiologies were noted as contributory with no attempt made by the investigators to rank their relative contribution or speculate regarding possible causal linkages between the categories noted.

Table 1. Distribution of types of cerebral palsy

CP Type	Number (%) (N = 217)
Spastic quadriplegic	77 (35.5%)
Spastic hemiplegic	*68 (31.3%)
Spastic diplegic	39 (18.0%)
Mixed	12 (5.5%)
Ataxic-hypotonic	12 (5.5%)
Spastic monoplegic	5 (2.7%)
Dyskinetic	2 (0.9%)
Worster-Drought	2 (0.9%)

* = Right hemiplegic (37); Left hemiplegic (31)

Abbreviations:
CP = Cerebral palsy

Results

Group Characteristics

Out of a total of 6,616 patients in the database, 217 (3.3%) were identified as having the cerebral palsy symptom complex. Not unexpectedly, a disproportionate number, 72 (33.2% of the total sample of cerebral palsy patients), were derived from the neonatal neurology clinic portion of the database because this clinic monitors neonatal intensive care unit survivors at high risk for neurodevelopmental sequelae. For patients treated in this clinic (N = 299), the frequency of observed cerebral palsy was 24.1% (72/299). For patients treated in other locales (i.e., neurology outpatient ambulatory clinic, hospital neurology private office, and suburban private office or nonneonatal/community source), the frequency of observed cerebral palsy in all patients referred for neurologic evaluation was 2.3% (145/6317). Of the 217 total cerebral palsy patients, the sex distribution was 129 males (59.4%) and 88 (40.6%) females, and the gestational age distribution was 96 preterm (44.2%) and 121 (55.8%) term. All patients underwent CT imaging. If cerebral dysgenesis/periventricular leukomalacia was suspected subsequent to CT, most further underwent MRI study.

Type of Cerebral Palsy

The distribution of patients among the types of cerebral palsy is listed in Table 1. Overall, the most common type observed in this sample was spastic quadriplegic (77, 35.5%). Of the 68 with a spastic hemiplegic cerebral palsy variant, the majority (37, 54.4%) were right-sided.

The frequency distribution for types of cerebral palsy according to sex, gestational age, and source (i.e., neonatal neurology clinic or not) is presented in Table 2. The relative frequency of each cerebral palsy type observed was similar in the sex and gestational age stratifications to that observed overall, with the exception of spastic diplegia, which was more frequent among preterm than term patients (30.2% versus 8.3%). We fitted a generalized logits model, using three categories for the response variable (diplegia, quadriplegia, hemiplegia) and three explanatory variables (sex, preterm/term, source of patient). The odds ratio for the prevalence of spastic diplegia compared with spastic quadriplegia among preterm versus term children was 3.77 (confidence interval = 1.58-8.98).

The profile of cerebral palsy type observed in the patients first treated in the neonatal neurology follow-up clinic (high-risk neonatal population) was markedly different than that observed in the community source (nonneonatal)–derived patients. In the neonatal clinic–source patients (N = 72), more than half manifested a spastic quadriplegic cerebral palsy (40/72, 55.6%) compared with only 25.5% (37/145) of patients with cerebral palsy from other sources. Spastic hemiplegic cerebral palsy was the most common variant observed in the community source–group population at 36.6% (53/145) compared with 20.8% (15/72) for spastic hemiplegia in the neonatal-source group. The odds ratio for spastic diplegia versus spastic quadriplegia among community-source patients compared with high-risk neonatal-source patients was 3.38 (confidence interval = 1.38-8.27), and versus spastic hemiplegia, the corresponding odds ratio was 3.45 (confidence interval = 1.66-7.16).

Table 2. Distribution of types of cerebral palsy by sex, gestational age at birth, and source of patient recruitment

	Sex		Gestational Age		Patient Source	
CP Type (N)	Male N = 129 (%)	Female N = 88 (%)	Premature N = 96 (%)	Full-Term N = 121 (%)	Neonatal N = 72 (%)	Community N = 145 (%)
Spastic quadriplegic (77)	46 (35.7%)	31 (35.2%)	34 (35.4%)	43 (35.5%)	40 (55.6%)	37 (25.5%)
Spastic hemiplegic (68)	41 (27.1%)	27 (30.7%)	25 (26%)	43 (35.5%)	15 (20.8%)	53 (36.6%)
Spastic diplegic (39)	24 (18.6%)	15 (17.1%)	29 (30.2%)	10 (8.3%)	8 (11.1%)	31 (21.4%)
Mixed (12)	6 (4.7%)	6 (6.8%)	5 (5.2%)	7 (5.8%)	3 (4.2%)	9 (6.2%)
Ataxic (12)	7 (5.4%)	5 (5.7%)	3 (3.1%)	9 (7.4%)	2 (2.8%)	10 (6.9%)
Spastic monoplegic (5)	4 (3.1%)	1 (1.1%)	0	5 (4.1%)	3 (4.2%)	2 (1.4%)
Dyskinetic (2)	1 (0.8%)	1 (1.1%)	0	2 (1.7%)	0	2 (1.4%)
Worster-Drought (2)	0	2 (2.2%)	0	2 (1.7%)	1 (1.4%)	1 (0.7%)

Abbreviations:
CP = Cerebral palsy

Table 3. Distribution of observed diagnoses

	Single Cause	*Multiple Causes Attributed
PVL	30 (13.8%)	54 (24.9%)
Asphyxia	27 (12.4%)	47 (21.7%)
Cerebral dysgenesis	37 (17.1%)	37 (17.1%)
Intracranial hemorrhage	12 (5.5%)	28 (12.9)
Vascular	20 (9.2%)	21 (9.7%)
Infection	11 (5.1%)	14 (6.5%)
Trauma	—	4 (1.8%)
Atrophy	4 (1.8%)	4 (1.8%)
Toxins	3 (1.1%)	6 (2.2%)
*Multiple causes	34 (15.7%)	—
Total causes identified	178	254
Unknown	39 (18%)	39 (18%)

* For 141 cases, a single diagnosis was observed; for 34 cases, multiple diagnoses were observed, 32 with two diagnoses, three with three diagnoses. Multiple causes observed are attributed in the last column to each case in which a particular diagnosis was noted. Number in parenthesis refers to percentage of all cases; $N = 217$.

Abbreviations:
PVL = Periventricular leukomalacia

Etiologic Determination

With respect to etiologic determination, an underlying diagnosis was determined in 178 of 217 (82.0%) of patients. For the vast majority, a single etiology was identified (144/217, 66.4%); however, for 31 patients (14.2%), two etiologies were identified, and for three patients (1.4%), three etiologies were identified. Thus, for only 39 patients (18.0%), identification of an underlying etiology subsequent to detailed neurologic evaluation and appropriate laboratory testing remained elusive. The spastic diplegic cerebral palsy type accounted for 16/39 (41%) of those in whom no etiology was evident, whereas spastic hemiplegia accounted for 13/39 (33%) and spastic quadriplegia, 7/39 (17.9%).

Overall, the most common etiology identified (multiple causes included with each single identifiable cause attributed to the patient affected) was periventricular leukomalacia in 54 patients (24.9%). As a single identifiable cause, the most common cause observed was cerebral dysgenesis in 37 patients (17.1%). The distribution of observed etiology (single and multiple) is presented in Table 3. A listing of all single and multiple groups of causes identified and their frequency is included in the appendix.

Etiology identified varied according to specific type of cerebral palsy and is summarized in Table 4. Among each group (where $N > 10$), the most frequently observed diagnosis in each cerebral palsy type was (1) spastic quadriplegic (intrapartum asphyxia, 25; 32.5%), (2) spastic hemiplegic (vascular, 18; 26.5%), (3) spastic diplegic (periventricular leukomalacia, 21; 53.9%), (4) ataxic-hyptonic (cerebral dysgenesis, 11; 91.7%), and (5) mixed (spastic and dyskinetic) (asphyxia, 6; 50.0%). No etiology was evident in seven (9.1%) individuals with spastic quadriplegia, 13 (19.1%) individuals with spastic hemiplegia, 16 (41.0%) with spastic diplegia, and one (8.3%) with the ataxic-hypotonic cerebral palsy variant. An etiology was evident in all cases of mixed cerebral palsy and Worster-Drought syndrome.

A generalized logits model was used to analyze three categories of outcome (i.e., cerebral palsy-type of diplegia, quadriplegia, and hemiplegia) and three explanatory variables representing categories of common diagnoses (periventricular leukomalacia, asphyxia, and others). When compared with spastic quadriplegia, spastic diplegia was more often associated with periventricular leukomalacia than with other diagnoses (odds ratio = 4.96; confidence interval = 1.28-19.18). When compared with spastic diplegia, spastic quadriplegia was more often associated with intrapartum asphyxia (odds ratio = 6.10; confidence interval = 1.44-25.8). When spastic hemiplegia was compared with spastic quadriplegia, spastic hemiplegia was less often associated with intrapartum asphyxia compared with other diagnoses (odds ratio = 0.20; confidence interval = 0.06-0.72).

Among males, the etiology most frequently observed (multiple causes included with each identifiable cause attributed to the patient affected) was periventricular

Table 4. Relative frequency distribution of diagnoses identified according to cerebral palsy type

	Spastic Quadriplegia	Spastic Hemiplegia	Spastic Diplegia	Mixed	Ataxic-Hypotonia
#1 Etiology	Asphyxia (32.5%)	Vascular (26.5%)	PVL (53.9%)	Asphyxia (50%)	Dysgenesis (91.7%)
#2 Etiology	PVL (29.9%)	PVL/intracranial hemorrhage (14.7%)	Intracranial hemorrhage (15.4%)	Toxins (16.7%)	—
#3 Etiology	Dysgenesis (18.2%)	Dysgenesis (13.2%)	Asphyxia (12.8%)	—	—
#4 Etiology	Intracranial hemorrhage/ infection (14.3%)	Asphyxia (11.8%)	Toxins (7.7%)	—	—
Unknown (%)	9.1%	19.1%	41%	—	8.3%

Number in parenthesis refers to percentage of all patients with particular cerebral palsy. Because of attribution of cases with multiple diagnoses identified, sum of percentages may exceed 100%.

Abbreviations:
PVL = Periventricular leukomalacia

Table 5. Diagnostic profile according to source of patient

	Community	High-Risk Neonatal
#1 Etiology	PVL (28.2%)	Asphyxia (32.9%)
#2 Etiology	Dysgenesis (20%)	Intracranial hemorrhage (23.6%)
#3 Etiology	Asphyxia (14%)	PVL (18.1%)
#4 Etiology	Vascular (10.3%)	Infectious (12.5%)
Unknown (%)	24.8%	4.2%

Abbreviations:
PVL = Periventricular leukomalacia

leukomalacia (38 or 29.5%). Among females, the most frequent etiology was cerebral dysgenesis (20 or 22.7%). For males, an underlying etiology was not evident in 23 individuals (17.8%), which compared with an almost identical figure of 18.2% (16) in females.

The etiologic distribution with respect to relative frequency was different whether a patient was treated initially in the high-risk neonatal follow-up clinic or in another locale, reflecting patients' diverse cerebral palsy type of profile described above (Table 5). In the neonatal follow-up clinic the most frequent etiology documented was intrapartum asphyxia (32.9%). This etiology was in contrast to that observed in the community source patient, in which the most frequent etiology observed was periventricular leukomalacia (28.1%). Furthermore, an inability to determine an underlying etiology in community-source patients occurred almost six times as frequently (24.8%) as in the patients treated initially in the high-risk neonatal follow-up clinic (4.2%).

Bivariate analysis (χ^2) was performed to determine the predictive value of clinical features observed at initial assessment in successfully identifying an underlying etiology. Statistically significant variables identified then underwent multivariate logistic regression analysis. This analysis with odds ratios from the bivariate analysis is summarized in Table 6. The variables reaching statistical significance ($P < 0.05$) included microcephaly, neonatal difficulties (regardless of patient source), prior/coexisting epilepsy, and neonatal follow-up patient source. Factors not associated with successful etiologic determination in this analysis included sex and gestational age. The results did not change when a multivariate logistic regression model was used.

Table 6. Bivariate analysis of clinical features at intake and diagnostic together with corresponding odds ratio calculation

	Etiologic Yield	Odds Ratio (Confidence Interval)	χ^2 *P* Value
Microcephaly, $N = 84$	94.1%	5.32 (1.98–14.26)	0.0003
History of neonatal difficulties, $N = 121$	90.1%	3.55 (1.69–7.48)	0.0005
Epilepsy (prior or coexisting), $N = 55$	94.6%	4.95 (1.46–16.8)	0.0051
High risk neonatal source, $N = 72$	95.8%	5.94 (2.03–17.45)	0.0003

Neonatal difficulties refers to documentation of encephalopathy, intubation, or intervention (beyond observation) in a neonatal intensive care unit.

Discussion

The present study used a single child neurology practice source throughout a 10-year interval to address the question of identifying the relative frequency of various diagnoses in the cerebral palsy symptom complex. This paradigm of a single source has several advantages over use of a cerebral palsy registry for such a study. First, a consistent definition for cerebral palsy was applied, whereas considerable interobserver variation has been demonstrated in the use of registries [19]. Furthermore, the single practice source provided assurance that each patient underwent the same systematic comprehensive evaluation with reference to possible etiologic determination. This evaluation included a detailed neurologic evaluation and physical examination, together with imaging (CT and MRI) investigations. Such a process would not be the case in a cerebral palsy registry in which cases are entered from many sources (including nonmedical ones) lacking the consistent application of a diagnostic evaluation [19]. Similarly, the single practice source also provides for internal consistency regarding the definitions for the different etiologic categories and the criteria necessary for their identification. The recent time interval for this study allowed its data to offer a contemporary perspective of cerebral palsy; most articles addressing this specific issue predate the consistent availability of modern imaging (i.e., CT and MRI) technology.

Given the single practice source of patients for this study, concern can be raised regarding the representativeness of the sample under study with reference to the population of individuals with cerebral palsy as a whole in the potential local referral network (i.e., province of Quebec). A local survey of pediatric primary practice providers indicated that the vast majority refer their patients with physical impairment for subspecialty (i.e., neurologic) evaluation [20]. Indeed, such an evaluation is a necessary precursor in the Quebec milieu for the provision of pertinent rehabilitation and support services. Furthermore, the presence of a single comprehensive provincial payer system for health and rehabilitation services, with no additional costs to the individual patient, provides no economic barriers to healthcare access (i.e., specialty evaluation and requested laboratory investigations). Furthermore, the representativeness of the sample is suggested by the following characteristics: preponderance of males (59.4%), term born (55.8%), community source (66.8%), spastic cerebral palsy (87.5%), and right (as opposed to left) hemiplegic (54.4%) individuals, coinci-

dent with that reported in other cerebral palsy samples typically drawn from cerebral palsy registries [8-19].

There has been emphasis on the identification of prenatal and perinatal risk factors for later cerebral palsy, which has been of considerable benefit in furthering our understanding of potential mechanisms of pathogenesis for this symptom complex. However, to quote Ounsted, "risks are not causes" [21]. Our emphasis in this study has been on the identification of the actual etiologic spectrum and the causes' relative frequency in a consecutive series. Identifying specific etiologies and their relative frequency is of considerable importance with reference to prevention, intervention, and treatment strategies. At the individual case level, causal identification provides answers to questions regarding recurrence risks, may limit further potentially unnecessary testing, and empowers the family (and child) as an autonomous unit [22].

Our study reveals that in only a small minority of contemporary cases of cerebral palsy is a cause not identified (18%) and that the percentage that is unknown varies considerably, depending on the type of cerebral palsy under study. Unknown causes were highest for the spastic diplegic subtype. In our sample, diagnostic yield for this subtype was different whether the child was born preterm (21/29, 72.4%) or at term (2/10, 20%). For the majority of cases (110/144) in which a cause could be identified, a single etiology was responsible. In the remainder (34/144, 23.6%), two or, rarely, three etiologies were found to be contributory to the occurrence of cerebral palsy. This observation confirms recent speculation that many causes may be operative [23].

A major issue historically has been quantifying the role played by intrapartum asphyxia in causing cerebral palsy. Our study reveals that it is operative in only a minority of cases: 12.4% as a single cause and 21.7% where asphyxia and other mechanisms are attributed. Asphyxia as an etiologic factor varied among subtypes of cerebral palsy. These figures were obtained by rigid application (excluding the need for a specific cerebral palsy subtype) of the contemporary consensus definition for attributing asphyxia as a cause for cerebral palsy [18]. The relatively high value for the mixed cerebral palsy variant is not surprising, given the pathogenetic linkage of this cerebral palsy variant to severe acquired injury to deep gray-matter structures (status marmoratus) [24]. Asphyxia as a causal etiology is not, however, restricted just to the spastic quadriplegia and dyskinetic subtypes [18], which suggests that the British Medical Journal consensus criteria, which limit causal attribution of asphyxia to these two subtypes, may be too restrictive.

Our observation that intrapartum asphyxia is a minority cause for cerebral palsy (approximately one-fifth of cases) confirms that which has been documented [10-12]. The figure for asphyxia as an etiologic cause was remarkably similar whether the child was born at term (26/121, 21.5%) or preterm (21/96, 21.9%). The observation of cerebral palsy does not imply antecedent intrapartum asphyxia. Indeed, it remains far more likely that intrapartum asphyxia is not the cause of an individual's cerebral palsy. Thus, it is not surprising that increasing obstetric intervention has not resulted in a decline in cerebral palsy prevalence rate [6].

Our study does emphasize that the etiologic profile of cerebral palsy varies as a function of several factors: the type of cerebral palsy, the gestational age of the individual, and the referral source of the patient. Among the major cerebral palsy types, each exhibits a different etiologic spectrum. Furthermore, in only spastic diplegic cerebral palsy and in the uncommon types of mixed and ataxic-hypotonic cerebral palsy did a single etiology reach the threshold of being a majority cause for that specific cerebral palsy type.

Few articles have addressed the issue of the etiologic spectrum with reference to cerebral palsy type. Such studies have usually been done from the perspective of estimating the percentage caused by intrapartum asphyxia alone. Drawing from children identified through the collaborative perinatal study of the National Institute of Neurological Communicative Disorders and Stroke (1959-1996), Naeye et al. [25] identified intrapartum asphyxia as the cause of 6% of nonquadriplegic cerebral palsy, with over 60% (as opposed to our 18%) of cases not exhibiting an identifiable cause. Stanley et al. [8], using the Western Australia cerebral palsy registry, identified intrapartum asphyxia as a cause in 24% of quadriplegic cerebral palsy patients (of whom a sixth actually had mixed cerebral palsy). The majority of cases remained unexplained in this cerebral palsy registry–drawn study. In a study of patients from the mid-1970s and investigating the etiology of spastic diplegia in the preroutine imaging era [26], prenatal factors, as opposed to intrapartum or postpartum events, were emphasized as causally related to this cerebral palsy type. In a study of term hemiplegic cerebral palsy [27], the etiologic spectrum in descending order of frequency included periventricular leukomalacia (37%), cerebral dysgenesis (17%), and vascular causes (16%). This finding is in contrast to that of a more recent study of children with hemiplegic cerebral palsy [28] in which 46.2% (19/41) of the causes were vascular in origin, followed by periventricular leukomalacia (34.2%, 14/41) and cerebral dysgenesis (12.9%, 5/41). The latter study has a similar profile to that documented in our study, with the exception of the relative prominence in our study of intracranial hemorrhage as a cause of hemiplegic cerebral palsy. A recent study by Hagberg et al., who used a population-based approach from Western Sweden, revealed a similar etiologic yield of 81% [29]. Birth asphyxia was identified as an etiologic cause in 28% of cases in this study. Etiologic causes were not specified according to cerebral palsy type in this study, and neither was there any attempt to identify clinical features that may have suggested successful etiologic determination.

Etiologic profile in our study was also different in terms of referral source. Not surprisingly, those children evalu-

ated in the context of a high-risk neonatal follow-up clinic exhibited a profile highlighting etiologies with considerable acute neonatal morbidity with an enhanced risk for eventual long-term sequelae. For patients treated in an ambulatory community–derived context, an etiology could not be identified in 24.8% of cases (the highest for any stratification attempted), which would suggest different strategies for assessment and emphasis for etiologic determination in these two population groups and imply a larger role for detailed imaging studies in the community-derived group of patients. The majority of individuals with cerebral palsy are derived from seemingly low-risk community-based populations.

The etiologic categories used in this study are broadly defined and cannot be considered end points in themselves (i.e., prime movers). Recent efforts have been directed at identifying prenatal factors that may predispose an infant to the occurrence of intrapartum asphyxia [6,11,30]. Similarly, hematologic abnormalities have been documented in a subset of children with a vascular event as a cause for their cerebral palsy [31]. Likewise, genetic or intra-uterine factors have been elucidated as being responsible for the occurrence of a cerebral dysgenesis [32]. Asphyxia may lead to periventricular leukomalacia or intraventricular hemorrhage [33], suggesting that for those cases with multiple causes grouping these entities ($N = 16$), asphyxia may act as the prime mover. Our observation that five categories of etiology (periventricular leukomalacia, intrapartum asphyxia, cerebral dysgenesis, intracranial hemorrhage, and vascular) are responsible for the majority of all observed etiologies of cerebral palsy identified suggests an emphasis for strategies of prevention, intervention, and treatment. Research efforts designed to minimize cerebral palsy need to address the identification of factors that initiate these pathogenetic mechanisms or minimize their injurious effects. Research should also attempt to continue to diminish that group of individuals with cerebral palsy with unknown cause. Additionally, factors that underlie individual resiliency and modify eventual outcome need to be identified [34].

The design of our study permitted the identification of clinical factors evident on initial evaluation or physical examination that may suggest to the clinician that an etiologic search would be successful. The factors so identified included microcephaly, epilepsy, neonatal difficulties (regardless of the source of the patient), specific cerebral palsy type (quadriplegic or mixed, nondiplegic) and the actual source of patient referral (high-risk follow-up clinic). Similar clinical features associated with greater etiologic yield have been documented in other childhood developmental disabilities, specifically global developmental delay [35] and isolated motor delay [36].

Our study's findings further strengthen our evolving conception of cerebral palsy as an etiologically heterogeneous symptom complex. It clearly is not a unitary disease, and its complexity will render more difficult efforts to prevent and minimize this childhood disability. For most children with cerebral palsy, a careful search can reveal a possible cause; however, much work needs to be done in elucidating the prime movers that are the original source(s) of these mechanisms.

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Appendix

List of Identified Diagnoses

Asphyxia 27
Asphyxia/infection 2
Asphyxia/intracranial hemorrhage 3
Asphyxia/intracranial hemorrhage/periventricular leukomalacia 1
Asphyxia/intracranial hemorrhage/Trauma 1
Asphyxia/Periventricular leukomalacia 11
Asphyxia/vascular 1
Atrophy 4
Cerebral dysgenesis 37
Infection 11
Infection/intracranial hemorrhage 1
Intracranial hemorrhage 12
Intracranial hemorrhage/Periventricular leukomalacia 8
Intracranial hemorrhage/Trauma 2
Unknown 39
Periventricular leukomalacia 30
Toxins 3
Toxins/Periventricular leukomalacia 3
Vascular 20

Cerebral dysgenesis (n=37)
Cerebellar hypoplasia 11
Agenesis of corpus callosum 6
Lissencephaly pachygyria 5
Focal cortical dysplasia 5
Bilateral perisylvian polymicrogyria 3
Pontocerebellar atrophy 2
Dandy Walker 1
Walker Wurberg syndrome 1
Holoprosencephaly 1
DeMorsier/polymicrogyria 1
Schizencephaly 1

Infections (n=14)
TORCH 5
E. coli meningitis 3
Group B streptococcal meningitis 1
Fungal meningitis 1
Campylobacter meningitis 1
Pneumococcal meningitis 1
Hemophilus influenza meningitis 1
Sepsis 1

Intracranial hemorrhage (n=28)
Intraventricular hemorrhage 24
Intracerebral hemorrhage 4

Toxins (n=6)
Cocaine 3
Bilirubin 2
Alcohol 1