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Analysis of Clinical Features Predicting Etiologic Yield in the Assessment of Global Developmental Delay

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ABSTRACT

OBJECTIVE. Global developmental delay is a common reason for presentation for neurologic evaluation. This study examined the role of clinical features in predicting the identification of an underlying cause for a child's global developmental delay.

METHODS. Over a 10-year inclusive interval, the case records of all consecutive children <5 years of age referred to a single ambulatory practice setting for global developmental delay were systematically reviewed. The use of clinical features in predicting the identification of a specific underlying cause for a child’s delay was tested using χ² analysis.

RESULTS. A total of 261 patients eventually met criteria for study inclusion. Mean age at initial evaluation was 33.6 months. An underlying cause was found in 98 children. Commonest etiologic groupings were genetic syndrome/chromosomal abnormality, intrapartum asphyxia, cerebral dysgenesis, psychosocial deprivation, and toxin exposure. Factors associated with the ability to eventually identify an underlying cause included female gender (40 of 68 vs 58 of 193), abnormal prenatal/perinatal history (52 of 85 vs 46 of 176), absence of autistic features (85 of 159 vs 13 of 102), presence of microcephaly (26 of 40 vs 72 of 221), abnormal neurologic examination (52 of 71 vs 46 of 190), and dysmorphic features (44 of 84 vs 54 of 177). In 113 children without any abnormal features identified on history or physical examination, routine screening investigations (karyotype, fragile X molecular genotyping, and neuroimaging) revealed an underlying etiology in 18.

CONCLUSIONS. Etiologic yield in an unselected series of young children with global developmental delay is close to 40% overall and 55% in the absence of any coexisting autistic features. Clinical features are readily apparent that may enhance an expectation of a successful etiologic search. Screening investigations may yield an underlying cause.

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Key Words
etiology, developmental delay, evaluation

Abbreviations
GDD—global developmental delay
PDD—pervasive developmental delay
PVL—term periventricular leukomalacia
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GLOBAL DEVELOPMENTAL DELAY (GDD) is one of the most common reasons for referral to a pediatric subspecialty (ie, neurology and developmental pediatrics). It is defined as a significant delay in ≥2 of the major developmental domains (gross/fine motor, speech/language, cognition, social/personal, and activities of daily living), although most affected patients have impairment evident in all 5 of the domains.\(^1\)\(^2\) GDD is a term that is often reserved for children below the age of 5 years. The prevalence of GDD in the pediatric population is not precisely known; however, estimates of affected children range between 1% and 3%.\(^3\)

The role of the subspecialist when assessing these patients is several-fold: to verify that GDD does indeed exist, carefully search for an underlying etiology, provide access and referral to adequate therapeutic and rehabilitation resources, and, when possible, offer prognostication.\(^4\) Clarification of the underlying cause for a child’s delay can assist the neurologist in providing an estimation of the child’s ultimate developmental potential and possible recurrence risk in siblings and, in occasional cases, can lead to specific treatment and intervention.

The reported yield of the search for an underlying etiology is extremely variable, ranging from 10% to 81%.\(^4\)\(^-\)\(^8\) Several factors account for the wide range in documented etiologic yield, including the rigor and consistency of applied investigations, the degree of technological sophistication, and characteristics of the study population. A recent prospective study performed in our center identified an etiology in 55% of 80 children with GDD.\(^9\) However, precision of this estimate was limited by sample size.

The optimal approach for workup of a child with GDD remains unclear. There is considerable uncertainty with respect to the extent of investigations that should be undertaken. A recent practice parameter has reviewed the available evidence concerning the value of diagnostic testing in the initial evaluation of a young child with GDD and has suggested an algorithm for an evidence-based approach.\(^1\)\(^0\) However, the suggestion of definitive recommendations has been hampered by the lack of large-scale studies that have examined the clinical features of children with GDD, the etiologic yield of specific diagnostic tests, and which features on history and physical examination may enhance the expectation of an etiologic yield. Therefore, we undertook a large-scale retrospective study of a community-derived ambulatory clinic population to evaluate the etiologic yield of GDD and to examine which clinical features at initial evaluation predict the successful identification of an underlying cause for GDD.

METHODS
A comprehensive database containing all of the patients seen in a single academic pediatric neurology practice during a 10-year inclusive interval between July 1, 1994, and June 31, 2004, was systematically scanned. This database contains demographic, diagnostic, and treatment information for each patient. All of the information was collected at the time of initial patient contact and updated regularly at each subsequent patient visit, or when the results of diagnostic investigations became available. Patients contained in this database have been seen in 4 different locales: (1) a university hospital-based outpatient clinic (together with resident house staff); (2) a university hospital-based private office; (3) a university hospital-based neonatal neurology clinic; and (4) a suburban private consultation practice.

This database was scanned for all patients with a diagnosis of “global development delay,” “autism,” “pervasive developmental delay” (PDD), “pervasive developmental delay not other specified,” or “developmental delay.” The chart of each patient was then reviewed for eligibility in the study to minimize any possible mistakes in original diagnosis or data entry. Patients below the age of 5 years with a final diagnosis of GDD were included. Subjects were excluded if (1) the assessment was not in the context of a general pediatric neurology ambulatory setting (ie, patients were seen in the context of the subspecialty neonatal neurology clinic or neurogenetics clinic), (2) they had already been evaluated by another neurologist for developmental delay (ie, second opinion sought), (3) requested investigations were not completed, or (4) a diagnosis of an autism syndrome (PDD) had been made, based on the application of Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition, criteria.

Each child had been assessed by the same pediatric neurologist (M.I.S.). At the first evaluation, a thorough standardized history and physical examination was performed, and laboratory testing was individualized based on the suspected etiology. Neuroimaging investigations were obtained on all of the patients who exhibited physical findings, such as microcephaly, asymmetry, and long tract signs on neurologic examination, or who had a history of possible perinatal asphyxia. A metabolic workup was performed on all of the patients who had a family history of GDD, dysmorphic features, parental consanguinity, or episodic decompensation or regression. Most children also received neuroimaging, as well as a karyotype analysis (typically standard G-banding during the first years of study entry, then high resolution prophase banding subsequently) and fragile X molecular testing on a routine screening basis, including those without any evident historical or physical examination features.

Hospital charts were reviewed, and the following variables of interest were recorded: age at initial specialty assessment, age when delay first suspected, family history, developmental history, presence of autistic features or seizures, findings on neurologic examination, head
circumference, investigation results including imaging, blood tests, genetic testing, and the final etiology assigned. Autistic features were considered to be present if repetitive behaviors, avoidance of eye contact, desire for sameness, social isolation, and lack of imaginative play were features that were evident on either history or neurodevelopmental examination. Patients who satisfied the full criteria for the diagnosis of an autism syndrome (PDD) according to Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition, criteria were, however, not included in the study cohort presented herein.

Intrapartum asphyxia was diagnosed based on a combination of a history and objective documentation of various intrapartum complications (ie, fetal heart rate changes [late decelerations, loss of variability, and profound bradycardia], sentinel event, meconium staining, or acidic cord pH), subsequent moderate-to-severe neonatal encephalopathy, other organ or systemic dysfunction, and compatible electrophysiologic and neuroimaging changes as per recent consensus statements.\textsuperscript{11,12}

At a minimum, moderate to severe neonatal encephalopathy needed to be present together with at least 3 other criteria for this diagnosis to be made. Toxin exposure was diagnosed based on historical data and objective physical findings (eg, fetal alcohol syndrome- as per established Centers for Disease Control and Prevention criteria with independent confirmation by a specialist in medical genetics). Chromosomal etiology referred to a genetic abnormality visible on karyotype analysis, fragile X molecular genotyping, or fluorescence in situ hybridization study. Genetic etiology referred to all other syndromes with known genetic cause. Term periventricular leukomalacia (PVL) was defined as radiologic evidence of PVL in the absence of known prenatal complications, prematurity, intrapartum asphyxia, or traumatic birth. Cerebral dysgenesis and leukodystrophy were defined by features on neuroimaging. Psychosocial deprivation was defined as evidence of parental neglect, abuse, or isolation as noted by a social welfare agency; the removal of the child from home environment by a social agency; or the copresence of a severe attachment disorder. Severity of GDD was stratified into mild, moderate, and severe categories according to the percentage of functional age documented by an evaluating rehabilitation specialist (eg, occupational therapist) using age-appropriate standardized measures of function and development compared with actual chronological age (ie, mild: 67%–100%; moderate: 33%–66%; and severe <33%).

$\chi^2$ analysis was used to determine whether the presence of each clinical feature was associated with a significant increase in the rate of etiologic yield. A $P \leq .05$ was used for establishing statistical significance.

Forward stepwise logistic regression analysis was used to examine the contribution of all clinical variables that best determined whether an etiology was identified. A cutoff of $P = .10$ was used for including particular variables into the model.

**RESULTS**

From the complete database, containing 5369 patients, the charts of 814 patients were selected based on the broad initial search terms. Of these 814 patients, 553 did not meet rigid application of our inclusion criteria. Reasons for exclusion included: age $\geq$5 (145 [26%]), initially seen in specialty neurogenetics or neonatal neurology clinics (117 [21%]), second opinion (75 [14%]), not seen initially in an ambulatory setting (49 [9%]), diagnosis of an autism syndrome (PDD; 30[5%]), incomplete testing (18 [3%]), absence of GDD (10 [2%]), and other (11 [2%]). Ninety-nine additional patients (18%) had multiple reasons for exclusion. This left 261 patients who were included in the study who were felt to represent a community-based sample of young children with GDD referred for subspecialty evaluation.

The mean age at initial evaluation was 2.8 ± 1.3 years. The mean age when delay was first suspected by the parents was 1.5 ± 0.9 years; therefore, the average latency from suspicion to eventual evaluation by a neurologist was 1.3 years. There were 193 males and 68 females, corresponding with a male/female ratio of 2.84:1. There were 34 (12.2%) of 261 with mild GDD, 112 (43.0%) of 261 with moderate GDD, and 115 (44.1%) of 261 with severe delay.

Overall, a cause was found in 98 (38%) of 261 children. The etiologic causes found are presented in Table 1. The most common etiologic groupings were: genetic syndrome/chromosomal abnormality (24 [24%]), intrapartum asphyxia (22 [22%]), cerebral dysgenesis (16 [16%]), psychosocial deprivation (11 [11%]), and toxin exposure (7 [7%]). The timing of etiology when determined was clearly perinatal in 22 of 98 (22%) and postnatal in 15 of 98 (15%) with the balance prenatal in origin. Perinatal etiology was intrapartum asphyxia, and postnatal etiologies were psychosocial deprivation, metabolic disorders, and leukodystrophy.

The factors associated with the eventual identification of an underlying cause are presented in Table 2. Factors predictive of eventual etiologic yield were female gender, abnormal prenatal/perinatal history, absence of any autistic features, presence of microcephaly, abnormal neurologic examination, and dysmorphic features. A family history of mental retardation or neurodevelopmental delay, the severity of GDD documented, the presence of a coexisting seizure disorder, and macrocephaly did not have an effect on the ability to eventually identify an underlying etiology.

In 113 children without any abnormal features identified on history or examination, screening investigations (karyotype, FMR1, and neuroimaging, typically) revealed an underlying etiology in 18 (16%) that was
not suspected previously. The laboratory testing undertaken in these patients overall is summarized in Table 3.

The univariate logistic models generated for each variable indicated that female gender, abnormal prenatal/perinatal history, absence of any minor autistic features, presence of microcephaly, abnormal neurologic examination, and dysmorphic features were significantly associated with etiologic yield. The combination of clinical features that led to the most predictive and parsimonious model on forward stepwise logistic regression analysis included female gender, abnormal prenatal/perinatal history, absence of any minor autistic features, and abnormal neurologic examination (see Table 4).

**DISCUSSION**

In our study, an etiology was determined in 38% of children with GDD overall and in 53% of children without minor autistic features. This is similar to, but slightly lower than, proportions reported in other studies. Studies at our center, including a retrospective chart review of 60 children with GDD and a prospective study over an 18-month inclusive period of 80 children with GDD (both of which excluded patients with an autistic spectrum disorder) found an etiology in 63% and 55%, respectively. A recent retrospective study in Turkey looking at 247 children with GDD identified an etiology in 63% of cases. Some of the differences between our study and previous studies can be explained by differences in methodology and referral population. First, a number of diagnoses included in the study by Ozmen et al., such as phenylketonuria and hypothyroidism, were not encountered in our population, because these would have been identified during the neonatal period with mandatory provincial routine screening. In addition,
syndromes that were obvious on early examination of morphology, such as Down syndrome, were not included in our study, because they are rarely referred for diagnostic workup of developmental delay in our center. Also, sample populations are different, with metabolic and genetic disease probably more prevalent in Turkey because of a documented higher incidence of parental consanguineous matings. It is unlikely that secular trends have had much effect on etiologic yield, because our current study did not find a significant difference in etiologic yield between the first 5 years and the second 5 years of the enrollment period (59 of 153 [38.5%] vs 39 of 108 [36%]; χ² = 0.16; P = .69).

The observation that an etiology for GDD can be found in over a third of children reinforces the notion that a referral to a subspecialist is worthwhile, given the potential ramifications of an etiologic diagnosis for recurrence risk estimation in the family, more accurate prognostication, and possible institution of specific therapeutic interventions. Of interest, we found that even in the absence of any abnormalities on history or physical examination, basic screening investigations, composed of neuroimaging (computed tomography or MRI), karyotype, and molecular fragile X testing, identified an etiology in 16% of cases. This lends support to the practice of routine neuroimaging and genetic screening investigations in all children with GDD, as outlined in the recent American Academy of Neurology GDD algorithm.

The main etiologies of GDD identified in our study were genetic syndromes/ chromosomal abnormalities, perinatal asphyxia, cerebral dysgenesis, psychosocial deprivation, and toxin exposure. Although there were a wide number of possible etiologies, only a small number of possible categories accounted for the majority of diagnoses, with these 5 categories representing 80% of all cases in which an etiology is found. This is similar to the most common etiologies reported in other series.

A considerable proportion of etiologies, including toxin exposure, psychosocial deprivation, in utero infection, and perinatal asphyxia, are theoretically potentially preventable. These etiologies represented more than one third (42%) of etiologies actually identified in children with GDD. Alcohol was the primary culprit of in utero toxin exposure (6 of 7 cases). This highlights the potential for prevention strategies that can be developed in our communities, such as alcohol treatment programs targeting women of childbearing age or preconceptional maternal interventions in socially at-risk environments.

Clinical factors that predicted etiologic yield were female gender, abnormal prenatal/perinatal history, absence of autistic features, presence of microcephaly, dysmorphisms, and abnormal neurologic examination. Some of these factors, such as abnormal prenatal/perinatal history, microcephaly, and an abnormal neurologic examination, would be anticipated as important clues to potential diagnoses and, therefore, their prediction of improved etiologic yield, if present, is not surprising. However, others are less predictable and are of interest for future study for validation.

Males were much less likely than females to have an underlying etiology discovered (30% vs 59% in females). It is known that males represent the majority of children with developmental delay, and, in our study, 74% of the children with GDD were males. The reasons for the disparity are not clear, but is likely partially because of unknown X-linked or X-limited conditions. There are already a number of known X-linked causes of developmental delay, which include the most common chromosomal cause of developmental delay (fragile X syndrome), as well as such entities as Coffin-Lowry syndrome, creatine transporter defects and oculocerebrorenal syndrome. Our results suggest that there are a greater number of as yet readily unidentifiable possible X-linked causes given current methodologies. An alternative explanation would be a gender-based male vulnerability to acquired conditions.

Children with autistic features were far less likely to have an identified underlying etiology. This had also been described in the smaller previous case series from our center. This may suggest that the identification of autistic features in a patient with GDD may indicate that an exhaustive investigation for underlying causes may not be fruitful. In addition, there is some controversy as to the nature of autistic spectrum disorders, with some suggesting that autism is a syndrome complex with multiple underlying etiologies, whereas others argue that it is a separate disease process of which the cause (or causes) are unknown. Our findings that an underlying etiology can rarely be found in children with global delay with associated autistic features perhaps argues for the latter view.

The presence of dysmorphic features has not consistently been found to be predictive of etiologic yield in previous studies. Previous studies where this issue was addressed featured a smaller number of children, and the conflicting results may reflect a lack of power of these earlier studies. Dysmorphic features may, how-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successful Identification of Underlying Etiology</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal neurologic examination</td>
<td>−1.42</td>
<td>0.36</td>
<td>0.24</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.04</td>
<td>0.35</td>
<td>2.83</td>
<td>.003</td>
</tr>
<tr>
<td>Abnormal prenatal/perinatal history</td>
<td>1.23</td>
<td>0.33</td>
<td>3.40</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Absence of autistic features</td>
<td>1.34</td>
<td>0.37</td>
<td>3.82</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Constant</td>
<td>−2.06</td>
<td>1.134</td>
<td>0.128</td>
<td>.070</td>
</tr>
</tbody>
</table>

α = 261; χ² = 95.27; P < .001.
ever, be predictive of genetic abnormalities, as well as antenatal toxin exposures, such as alcohol. In our study, the presence of dysmorphic features was associated with a higher likelihood of an abnormal genetic test result \( (12 \text{ of } 79 \text{ vs } 4 \text{ of } 170; \chi^2 = 14.8; P = < .001) \).

This study found no association between the severity of the delay and the identification of an underlying etiology. A child with mild delay is just as likely as a child with severe delay to have an identifiable underlying etiology. This finding has been reported previously.\(^9\)

Thus, subspecialty consultation is of potential use, regardless of the actual severity of GDD. The severity of the delay should not influence the actual vigor of etiologic evaluation.

It is important to note several limitations of this study. First of all, although data were collected prospectively, the analysis was retrospective in nature. Therefore, some of the limitations of retrospective studies apply, such as incomplete data assessment. Second, in some cases, a complete diagnostic panel was not ordered, resulting in missing data. Preexisting notions by clinicians as to potential diagnostic yield may lead to a self-fulfilling prophecy, resulting in information bias. Also, the sample population comes from a single neurologist’s practice in Canada, and results may not generalize completely to other populations where medical practice, expertise, referral patterns, accessibility to medical care, and societal factors may be different. Referral patterns may be an important determinant of the proportion of etiologic yield found in other settings. Previous determinations of our referral patterns have suggested that our clinic population was reasonably representative of the spectrum of the GDD in our local referral network.\(^4\) Our clinic population does not include entities identified during the mandatory Quebec newborn screening program (ie, hypothyroidism and amino acidopathies), as well as syndromic diagnoses that are readily made in the neonatal or early infantile period, such as Down syndrome. There are also some limitations as to the intensity of diagnostic workup. For example, none of our patients underwent subtelomeric chromosomal rearrangement screening studies, because these were not readily available locally during the enrollment period of our study. It has been estimated that these procedures detect abnormalities in 6.8% of patients with moderate or severe developmental delay and 1.1% with mild developmental delay.\(^16\)–\(^19\) If these studies were added to the routine workup, we would anticipate a higher etiologic yield than that obtained. Of note, accessibility to testing was not an issue in our center, because comprehensive government-mandated health insurance coverage provides for no economic barriers to testing. This is further evident by the very small number of children who were excluded from the study because of incomplete investigations.

A pragmatic approach, first suggested by Schaefer and Bodensteiner,\(^9\) was used in ascribing etiology. This approach conceptualizes etiology as a “specific diagnosis that can be translated into useful clinical information for the family, including providing information about prognosis, recurrent risks, and preferred modes of available therapy.”\(^7\) It is a conceptualization that is consistent with the recent Child Neurology Society and American Academy of Neurology practice parameter addressing this topic.\(^10\) Thus, some of the etiology used herein are heterogeneous and more pathogenic in description (eg, cerebral dysgenesis and term PVL) in which a causal connection to the child’s developmental delay can be strongly inferred. In addition, at the present time, often the “prime mover” for the observed etiology (eg, gene responsible for particular cerebral dysgenesis) is not yet known.

The results of our study suggest that a careful search for an underlying etiology in children with GDD is worthwhile, regardless of the severity of the delay or the absence of findings on history and physical examination. The presence of certain clinical features at initial evaluation increases the likelihood of the identification of an underlying etiology; however, their absence should not deter the clinician from pursuing screening investigations, such as neuroimaging and karyotype and fragile X testing. The results of this study links credence to consideration for prospective testing of a diagnostic algorithm.

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GENZYME’S DRUG FOR RARE ENZYME DEFICIENCY IS APPROVED

“Genzyme won federal approval yesterday to sell the first drug for Pompe disease, a rare inherited enzyme deficiency that destroys muscles and can kill infants by their first birthday. The drug, Myozyme, is the fourth developed by Genzyme to treat a rare enzyme deficiency under the incentives provided by the federal government to develop medicines for so-called orphan diseases. Genzyme officials said Myozyme, like the previous drugs, would cost about $200,000 to $300,000 a year on average, though significantly less for infants, who require less of the product. At those prices, sales could reach hundreds of millions of dollars annually, even though there are fewer than 10,000 people in the world with Pompe disease. Shares of Genzyme fell 3 cents, to $61.16 yesterday. . . . All 18 infants given Myozyme in a clinical trial—conducted from 2003 to 2005—lived until they were at least 18 months old, or about a year after starting treatment, and most are still alive today. In the past, nearly all of those babies would have died by 18 months of age. Still, 7 of the children needed a ventilator to breathe and 2 eventually died, one after 14 months of treatment and one after 25 months, according to the drug’s labeling information. And while muscle function improved in many of the infants, it was still below normal. Myozyme can also cause life-threatening anaphylactic—or allergic—reactions, according to a warning on its label.”


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