The authors make a good case for "working up" the young child with global developmental delay when the cause is not apparent. However, most of the recommended examinations and studies could be accomplished or ordered by a well-trained general pediatrician, and as the authors point out, cost containment is a significant concern. Perhaps consultation with a neurologist is not always needed in the evaluation of developmental delay in such children unless specific neurologic issues need to be addressed.—*J.M.G., Editor*

Diagnostic yield of the neurologic assessment of the developmentally delayed child

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Objective: **The aim of this study was to determine the etiologic yield of the neurologic assessment of a consecutive cohort of developmentally delayed children.**
Study design: **A retrospective chart review was carried out on all patients referred to a single university-based pediatric neurologist for evaluation of global developmental delay from July 1991 to December 1993. Patients referred because of isolated speech or motor delay or autism or those who had been previously evaluated by another neurologist were excluded.**
Results: **A total of 77 patients were identified; 47 were male, and 62 were referred by a pediatrician. Neurologic evaluation did not confirm global delay in 10, and 8 did not complete diagnostic evaluation; one child was included in both groups. Of the remaining 60, an etiologic diagnosis was suspected by the referring physician at the time of referral in 13. Although parents suspected a delay at a mean age of 0.66 (±0.69) year, children were examined by the neurologist at a mean age of 3.58 (±2.42) years. Twenty-five were mildly delayed, 23 were moderately delayed, and 12 were severely delayed. Diagnostic studies (history, physical examination, and selected investigations, including screens for metabolic disease, karyotype, fragile X testing, electroencephalography, and neuroimaging) yielded an etiologic diagnosis in 38 (63.3%) of the 60 patients. Etiologic categories included cerebral dysgenesis (16.7%), hypoxic-ischemic encephalopathy (10.0%), chromosomal abnormalities (10%), toxins (8.3%), metabolic disorders (5.0%), and neurocutaneous (3.3%), neuromuscular (3.3%), genetic/dysmorphic (3.3%), and epileptic (3.3%) syndromes. Etiologic yield was equivalent across categories and degree of developmental delay.**
Conclusion: **Referral to a pediatric neurologist and application of a selected battery of investigations yield etiologic findings with important implications with respect to management, prognosis, and recurrence risk estimate in a significant portion of globally delayed children. (J PEDIATR 1995;127:193-9)**

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Developmental delay is a common clinical problem in pediatrics, with an estimated prevalence of 10%.[1,2] Recent emphasis has been on the early identification of affected children so that they can benefit from early intervention programs.[3,4] An important additional goal in the evaluation of developmental delay in a child should be the determination of a specific reason for the child's disability. This would provide information regarding possible pathogenesis, prognosis, recurrence risks, and specific medical interventions,[5] the critical questions most often posed to the clinician by the families of these children. Traditionally, it has been thought that an etiologic diagnosis would more likely be determined among children with severe developmental delay. Milder delays were thought to be primarily the result of cultural or environmental influences rather than biologic variables.[6] Recent pathologic studies have challenged this assumption.[7]

Controversy exists within the literature regarding the extent of medical and laboratory investigations needed for evaluation of the developmentally disabled child.[3,5,8] Such controversy is important within the context of today's concerns about the costs of health care. Few data are available on the etiologic yield of a comprehensive evaluation using recent diagnostic advances; the most widely cited reference dates from the "pneumoencephalogram" era in neuroimaging.[9]

CT	Computed tomography
HIV	Human immunodeficiency virus
MRI	Magnetic resonance imaging
OT	Occupational therapy

The aim of this study was to determine the etiologic or diagnostic yield of the neurologic examination and pertinent laboratory investigations in a consecutive cohort of children referred to a pediatric neurologist for evaluation of developmental delay.

METHODS

Subjects

Inclusion criteria. All children referred to a single university-based pediatric neurologist (M.I.S.) for evaluation of developmental delay between July 1, 1991, and Dec. 31, 1993, were initially identified through a review of a comprehensive, standardized computerized database (Claris Filemaker Pro C), which includes all patients seen by this neurologist since he commenced practice. The database has multiple "fields" relevant to patient identification, history (including "reason for referral" and "age at onset"), diagnoses (neurologic and nonneurologic), and treatment. Developmental delay was the primary reason for referral noted in the referring physician's written request for neurologic consultation. Such a written request is a necessary precondition for neurologic evaluation in Quebec.

These patients were initially assessed either in a hospital-based private office, in a community pediatric clinic, or in an outpatient neurology clinic by the neurologist together with house staff. The purposes of the neurologic evaluation were (1) to confirm the presence of developmental delay, (2) to determine the cause, and (3) to provide referral and access to appropriate resources.

Exclusion criteria. Patients referred specifically for evaluation of autism, isolated motor delay, or isolated speech delay were excluded from data analysis. Also excluded were patients previously seen by another neurologist and seeking a second opinion, as well as those seen initially in consultation through the neurologist's participation in ambulatory subspecialty clinics (neurogenetics and neonatal neurology), because this would favor detection of an etiologic factor. Thus the patient sample constitutes a consecutive series of children referred to an ambulatory neurologic setting for evaluation of perceived developmental delay.

Operational terms. For the purposes of this study, developmental delay was defined as delay in two or more developmental domains (gross motor, fine motor, cognition, speech/language, personal/social, or activities of daily living). According to Schaefer and Bodensteiner,[5] "reference to etiology is made in the context of a specific diagnosis that can be translated into useful clinical information for the family, including providing information about prognosis, recurrence risks and preferred modes of available therapy." A causal relationship between the identified etiologic factor and the child's developmental disability was assumed.

Procedures. The charts of all patients in the sample were reviewed retrospectively by the neurologist after the assessment and laboratory investigations of all children in this cohort were completed. A patient information sheet was completed for each; this included name, gender, age when the parent(s) suspected a developmental delay, age at initial neurologic assessment, the specialty of the referring physician, whether an etiologic diagnosis was suspected by the referring physician and whether it was correct, the tests ordered by the neurologist, the type of delay documented clinically, the cause if known once investigations were completed, and whether the cause was confirmed by history, physical examination, or test results.

Standardized, age-appropriate occupational therapy and psychologic evaluations, obtained as part of the initial assessment of this cohort of patients, were also retrospectively reviewed by us. As part of the OT report, age equivalents were given for each of the developmental domains, and the psychologic assessments additionally provided intelligence quotients. On the basis of reports, patients were assigned to a category of either mild, moderate, or severe developmental delay. For the purposes of this study, mild developmental delay was defined as a delay of less than 33%

(i.e., when comparing overall functional age to chronologic age) or an IQ between 55 and 69. Moderate developmental delay comprised a delay of 34% to 66% or an IQ between 40 and 54. Severe developmental delay was defined as a functional age less than 33% of chronologic age or an IQ less than 40. If standardized OT or psychologic assessments were not obtained, the detailed observations of the neurologic consultation were reviewed and the patient was assigned to one of the aforementioned categories. At the time of the review of these assessments, we were unaware of the results of etiologic determination.

A survey form was mailed to all physicians who had referred these patients with developmental delay and were still practicing in the province (N = 43). This brief survey contained six questions with multiple answers: (1) What percentage of children with developmental delay in your practice do you refer to a pediatric neurologist for assessment? (seven levels of response, from none [0%] to all [100%]). (2) If you do not refer all your patients with developmental delay to a pediatric neurologist, which of the following criteria do you use to refer a patient? (3) Rank in order of importance the reasons for referring your patient with developmental delay to a pediatric neurologist. (4) Do you consider the determination of cause to be important? (four levels of response, from not important to very important). (5) Once investigations are completed, in what percentage of patients with developmental delay referred to a pediatric neurologist would you expect an etiologic factor to be determined? (seven levels of response, from none [0%] to all [100%]). (6) What is the majority of your practice (community-based, hospital-based, both equally, other)?

RESULTS

Sample characteristics. Within the 2½-year period, 77 children were referred to the pediatric neurologist with a primary diagnosis of developmental delay. Those subsequently excluded from analysis were those with only gross motor (n = 3) or speech delay (n = 2), with no clinical evidence of delay (n = 3), or in whom the delay had resolved by the time of the initial neurologic assessment (n = 2). Eight families elected not to complete all investigations requested, and their children were also excluded. One of the children was excluded for two reasons (isolated gross motor delay and incomplete investigations); therefore 17 children in all were excluded from the initial cohort. Analysis was carried out on the remaining 60 patients.

Of 60 patients, 41 (68.3%) were male. Pediatricians referred 47 children (78.3%), general/family practice physicians referred 9 (15.0%), and pediatric subspecialists referred 4 (6.3%). Of 60 children with developmental delay, 9 (15%) had autistic features. Although global developmental delay was the primary diagnosis in all 60 children, 48.3% (n =29) had one or more concurrent diagnoses. These included microcephaly (n = 13), behavior disorders (n = 10; attention deficit disorder, pervasive developmental disorder/emotional difficulties), seizure disorder (n = 6; partial complex, myoclonic, atypical febrile convulsion), tremor (n = 1), glaucoma (n = 1), diabetes mellitus (n = 1), optic atrophy (n = 1), failure to thrive (n = 1), and hypotonia (n = 1).

Table I. Etiologic determination within each category of developmental delay

Etiologic determination	Degree of developmental delay			
	Mild	Moderate	Severe	Total
Yes	15	15	8	38
No	10	8	4	22
TOTAL	25	23	12	60

Of the 60 patients, 44 (73.3%) had standardized OT and/or psychology assessments. The OT assessments were performed on average within 1 month of the neurologic consultation (mean 0.96, SD 3.58, n = 40), whereas psychologic evaluations were generally made within 6 months (mean 5.82, SD 6.46, n = 19). Sixteen patients were classified as mildly delayed, 20 as moderately delayed, and 8 as severely developmentally disabled. When the details of the neurologic consultation on the remaining 16 patients were included, 25 (41.7%) of the 60 were mildly delayed, 23 (38.3%) were moderately delayed, and 12 (20%) were severely delayed.

Table I summarizes the distribution of degree of delay with etiologic determination. The majority (78.9%) of children with etiologic diagnosis had mild to moderate developmental delay. Furthermore, the percentage etiologic yield across the three categories of delay was relatively constant, ranging from 60% to 67% ($X^2 = 0.21$, $df = 2$, $p = 0.90$). This lack of association between etiologic determination and degree of delay was further analyzed with the Mantel-Haenszel test, which showed no tendency toward an increased likelihood of determination of etiologic diagnosis with changing degree of delay ($p = 0.66$).

At the initial visit with the neurologist, parents were asked at what age they had initially suspected a developmental delay in their child. The mean age reported was 0.66 year (SD 0.69, median 0.5), which was consistent in the three office settings (mean range 0.60 to 0.72 year). These children were initially examined by the neurologist at a group mean of 3.58 years (SD 2.42, median 3.33, range 0.5 to 11.0). Therefore there was a mean delay between parental concern and the initial visit to the neurologist of 2.92 years (SD 2.36, median 2.50, range 0.5 to 10.5). This delay was most marked for patients referred to the neurology clinic (mean 3.19 years, SD

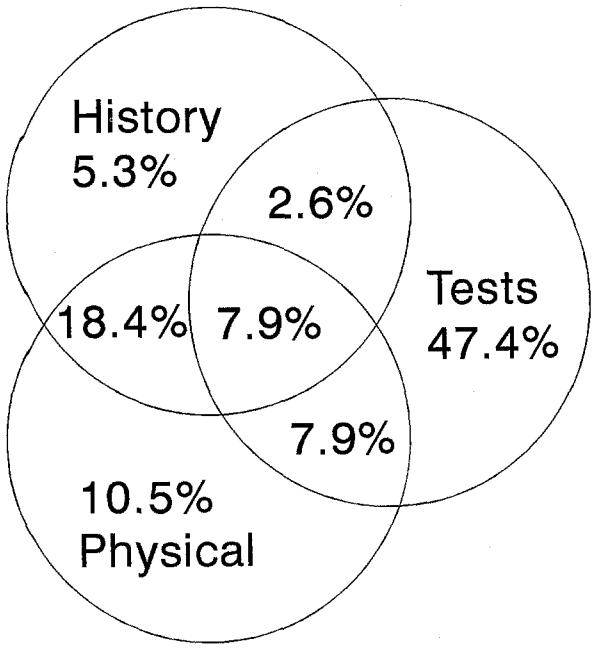

Figure. Relative contributions of the history, physical examination, and laboratory investigations to the determination of etiologic diagnosis.

3.17) and least prolonged for the community pediatric clinic (mean 2.57 years, SD 1.77) ($p > 0.05$).

A range of laboratory investigations were thought to be clinically warranted as part of the initial neurologic assessment of these children. Specific laboratory testing was individualized, and a "shotgun" approach was avoided; however, general guidelines were apparent in retrospect. If an etiologic diagnosis was not evident after the history and physical examination, a metabolic screen (capillary blood gas, lactate, ammonia, and serum amino acids), karyotyping that would include fragile X, and neuroimaging were ordered. Any suggestion of dysmorphology mandated karyotyping. Physical findings on neurologic examination (e.g,. tone abnormalities, microcephaly) or a history suggestive of hypoxic-ischemic encephalopathy warranted neuroimaging. With regard to evoked potentials, auditory brain-stem potentials were carried out if there was significant language impairment, and somatosensory evoked potentials were ordered if there was motor involvement. Electroencephalography was done routinely, with rare exceptions for obvious genetic syndromes or neuromuscular disorders. Table II summarizes the percentage of patients who underwent each investigation.

Determination of etiologic diagnosis. Once a history, physical examination, and battery of investigations were completed on the 60 patients, etiologic diagnosis was unknown in 22 (36.7%). In the 38 remaining children

Table II. Percentage of patients for whom each laboratory investigation was ordered

Investigations	Patients for whom each test was ordered (%)
Complete blood cell count	55.0
Capillary blood gas	65.0
Lactate	63.3
Ammonia	48.3
Serum amino acids	51.7
Urine organic acid	13.3
Thyroid function tests	26.7
Liver function tests	15.0
Karyotype	66.7
Fragile X	43.3
Electroencephalography	83.3
Auditory brain-stem potentials	51.7
Somatosensory evoked potentials	26.7
Computed tomography	85.0
Magnetic resonance imaging	18.3
Other tests	48.3

(63.3%; 95% confidence interval 50.7% to 75.9%), etiologic diagnosis was determined and fell into the following categories: 10 (16.7%) of 60 had cerebral dysgenesis (one or more of the following: cerebellar hypoplasia, agenesis of the corpus callosum, cerebral dysgenesis, heterotopia), 6 (10%) had hypoxic-ischemic encephalopathy, 6 (10%) had chromosomal aberrations (fragile X in 2, tetrasomy 15, chromosome 16 inversion, 22q- or 9p-), 5 (8.3%) had exposure to toxins (fetal alcohol syndrome in 3, prenatal multidrug exposure, or hepatic failure), 3 (5%) had metabolic disorders (pyruvate dehydrogenase deficiency in 2, Leigh disease), 2 (3.3%) had neurocutaneous disorders (neurofibromatosis type 1, tuberous sclerosis complex), 2 (3.3%) had neuromuscular disease (hereditary motor-sensory neuropathy type 1, congenital myotonic dystrophy), 2 (3.3%) had genetic syndromes (Weaver, Russell-Silver), and 2 (3.3%) had electrical/epileptic syndromes (progressive myoclonic epilepsy, electrical status epilepticus during slow-wave sleep). In 13 (21.7%) of 60 patients, an etiologic diagnosis had been suspected by the referring physician, and in all 13 it was confirmed. However, in a further 25 patients (41.7%) the etiologic diagnosis was ascertained by the neurologist.

When reviewing the charts, the neurologist coded whether the determination of etiologic diagnosis was confirmed by the history, the physical examination, or the findings on laboratory investigations. In 47.4% of cases, investigations alone provided the evidence needed for ascertainment of etiologic diagnosis. Information gathered from the history and physical examination together contributed to determination of etiologic diagnosis in 18.4% (history alone 5.3%, physical examination alone 10.5%). In 7.9%, all three components of the neurologic assessment were required (Figure).

Referring physicians' perspective. Forty-eight physicians had referred one or more patients to the neurologist for assessment of developmental delay during the designated period. Five no longer resided in the province of Quebec. Of the remaining 43, 39 (90.7%) responded to a brief survey on neurologic assessment of developmentally delayed children. In this cohort of physicians responding to the survey, 71.8% were community-based physicians; the others were either hospital-based or had a combination of both practices. Almost 75% of the physicians indicated that they referred all (28.2%) or most (43.6%) of their patients with developmental delay to a neurologist; this indicated that the sample was not likely to be biased toward more severe or more unusual cases.

The surveyed physicians were asked to rank five common reasons for referring children with developmental delay to a pediatric neurologist. A high priority (79.5%) was given to having the neurologist determine the cause, whereas a moderate interest was demonstrated in having him confirm the delay and manage the associated medical conditions. Relatively speaking, the least interest was shown in referring the patients to appropriate rehabilitation and community services and in providing family counseling. Ninety-five percent of the physicians indicated that determination of etiologic diagnosis was important to them (59.0% emphasizing that this was very important). There were diverse opinions among physicians regarding the expected number of patients in whom etiologic diagnosis could be established after neurologic investigation. The estimates given approximated a normal distribution; only a few indicated that etiologic diagnosis could be determined in 75% (estimated by 10.3% of physicians) or only in rare instances (<5% estimated by 7.7%). The estimates provided by 31 of 39 physicians ranged from 10% to 50% (median 25%).

DISCUSSION

In our consecutive cohort of children referred for evaluation of global developmental delay, an etiologic diagnosis was made in 63.3%. Previous series have been largely restricted to institutionalized cohorts of persons with severe mental retardation.[6, 10, 11] Limited data exist on determination of etiologic diagnosis in persons with mild mental retardation; these studies are hampered by the assumption that sociocultural factors play the major role, thus limiting the extent of investigations pursued.[5, 6] Given the referral pattern of the physicians responsible for our cohort, 72% of whom indicated that they referred all or most of their patients with developmental delay for neurologic assessment, and the determination that 80% of the patients had mild to moderate delay, we believe that our sample represents a reasonable cross section of the spectrum of developmental disability in our local referral network.

An etiologic yield of 63.3% exceeds previously published and inferred estimates. The improved yield likely represents the results of two factors: (1) improved diagnostic testing, specifically neuroimaging and metabolic, cytogenetic, and molecular techniques, and (2) an assumption that biologic factors underlie the majority of cases of developmental delay. The latter point emphasizes that the successful ascertainment of an underlying etiologic factor is a function of how hard one looks, as is strongly suggested by our finding that ascertainment of etiologic diagnosis was made possible in almost half of the cases by laboratory investigations alone. In only one third of the cases was the diagnosis made without the need for ancillary laboratory investigation.

The percentage etiologic yield was relatively constant across categories of degree of developmental delay. This indicates that a thorough investigational approach is justified in children across the spectrum of developmental disability. The clinician should not rely solely on the severity of delay to mandate investigations.

The broad number of etiologic categories identified raises the challenge of diagnostic vigilance. No single cause predominates, but two thirds of etiologic diagnoses can be accounted for by the categories of cerebral dysgenesis, hypoxic-ischemic encephalopathy, toxins, and chromosomal anomalies. Missing from our etiologic spectrum are trisomy 21 (Down syndrome),[12] aminoacidopathies, galactosemia, HIV encephalopathy, and lead intoxication, reflecting local newborn screening programs and sociodemographic factors.

Prenatal causes predominated, as expected.[13, 14] With regard to the postnatal cases, the metabolic disorders and one of the epilepsy syndromes identified are the result of genetic factors present at conception. In 15 of 60 total cases, an etiologic diagnosis provided crucial information regarding genetic counseling and recurrence risks (chromosomal anomalies, metabolic disorders, neurocutaneous syndromes, inherited neuromuscular disorders, and genetic syndromes). In 7 of 60 cases, the provision of an etiologic diagnosis significantly modified the medical management of the affected child (metabolic disorders, neurocutaneous syndromes, electrical/epileptic syndromes).

There has been some debate regarding the nature and extent of the laboratory evaluation of the child with global developmental delay. What is agreed is that such studies should be rational and selective, guided by history, physical examination, and potential diagnostic yield.[3, 5] Controversy surrounds the potential diagnostic yield of various investigations.

Studies addressing the yield of neuroimaging in patients with apparently idiopathic mental retardation employed pneumoencephalography/skull x-ray studies[9] or first-generation computed tomography as diagnostic modalities.[15-17] Not surprisingly, the diagnostic yield was low. This led

to recommendations that imaging was not necessary in all such persons, except for those with "substantial impairments."[8] CT was principally used, rather than magnetic resonance imaging, as the initial imaging test in our cohort, for reasons of local accessibility and cost. Given the technical superiority of MRI, it is not unreasonable to assume that the number of cases with cerebral dysgenesis is underestimated. This would be in keeping with the result of pathologic studies in which a high frequency of cerebral malformations has been documented[7] and with recent work that reveals a high frequency of subtle markers (cavum septum pellucidum,[18] macro cisterna magna,[19] and hypoplasia of the corpus callosum[20]) of cerebral dysgenesis in MRI studies of mentally retarded subjects.

Similar advances have occurred in cytogenetic techniques, resulting in improved diagnostic yield. Such improvements have included superior banding techniques,[21] fluorescent in situ hybridization,[22] and, with respect to the fragile X syndrome, rapid and low-cost molecular genotyping.[23] Previous studies have documented a high frequency of chromosomal anomalies among severely mentally retarded persons, with a lesser frequency in more mildly affected persons.

All six children with chromosomal abnormalities were mildly to moderately delayed by our criteria. Minor anomalies are frequent in this population, and often they are subtle and difficult for the physician to recognize.

Routine comprehensive metabolic screening in the developmentally delayed child has not previously been found to be informative[10, 24] and is not recommended at present. The past decade has seen the recognition of late infantile and childhood onset of variants of a spectrum of metabolic disorders[25] as well as the delineation of an increasing variety of phenotypes for disorders of subcellular organelles (e.g., mitochondria and peroxisomes).[26, 27] Variables that should prompt metabolic screening include an absence of apparent etiologic diagnosis after a detailed history, physical examination, karyotyping, and neuroimaging, as well as parental consanguinity, developmental regression, findings suggestive of an encephalomyopathy, or dysmorphism (e.g., storage or peroxisomal disorders). Recent reports have suggested that some cases of cerebral dysgenesis may have a metabolic basis.[28, 29] Within our cohort, laboratory investigation was selective, with no single test being used in all instances. Only karyotyping, electroencephalography, and neuroimaging (CT) were carried out in at least two thirds of children with global developmental delay. Two laboratory tests (neuroimaging and cytogenetic analysis), together with the history and physical examination, were most helpful in determining etiologic diagnosis in our series. The remaining etiologic diagnoses (metabolic disorders, neuromuscular syndromes, and electrical/epileptic syndromes) were made as a result of metabolic screening, electroencephalography, and electromyography. Although a minority of etiologic diagnoses were determined with these last tests, they had significant impact with regard to recurrence risk counseling and the modification of therapeutic intervention when a specific diagnosis was made.

On the basis of these results, we recommend that if an etiologic diagnosis is not readily apparent after a detailed history and physical examination, karyotyping and neuroimaging should be standard clinical practice for a child with global developmental delay. This concurs with the opinion recently expressed by Schaefer and Bodensteiner[5] in their comprehensive review. Although MRI is technically superior to CT, sufficient information is yielded by current CT methods to warrant its use in centers with limited access to MRI. In addition, careful consideration should also be given to molecular genotyping for the fragile X gene; this method is superior to cytogenetic analysis for a rather prevalent disorder with a wide range of phenotypic presentations and with important genetic implications.[30] Furthermore, a "low threshold" for metabolic screening and electroencephalography is suggested, given the genetic and therapeutic implications of accurate diagnosis of either a metabolic disorder[25] or an epilepsy syndrome. In our opinion, further detailed testing, such as organic acid analysis, determination of pyruvate levels, and enzymatic assay, should be pursued only when there is strong clinical suspicion or abnormal results on screening. The use of electroencephalography is also suggested within this clinical cohort, given the high frequency of coexisting seizure disorders and paroxysmal events that often raise a clinical suspicion of seizures.

In the current climate of cost containment, cost-benefit analyses are increasingly applied to all aspects of medical care, evaluation, and management.[31] Determining the financial costs associated with evaluation of the child with developmental delay is relatively easy, but quantifying the benefits of such an assessment proves more elusive. Establishing an etiologic diagnosis has significant implications with respect to recurrence risks and therapeutic imperatives that go beyond the academic interest of "knowing why." The information obtained through an etiologic diagnosis gives the families of disabled children the ability to make informed decisions regarding reproductive choices. Furthermore, an etiologic diagnosis provides for more accurate prognostication regarding the child's potential abilities and medical challenges. The recent imperative for early identification and early intervention in children with developmental disabilities raises the challenge of early, accurate etiologic diagnosis.[2, 8, 32]

This study suggests that optimal management of these children and their families should involve a comprehensive evaluation that employs both a detailed neurologic assessment and the judicious use of laboratory investigations. The

study also appears to validate the role of the pediatric neurologist in the assessment of the developmentally delayed child. The diagnosis of "global developmental delay" need not be the end point but can be a springboard for a careful search for causal factors. Further large-scale prospective studies are necessary to validate these findings and to determine the sensitivity and specificity of individual laboratory tests, so that investigations can be minimized without jeopardizing overall diagnostic yield.

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