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Original article

Etiologic determination of childhood developmental delay

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Abstract

To determine the etiologic yield in young children with developmental delay referred to sub-specialty clinics for evaluation. Over an 18-month period, all children less than 5 years of age referred to the ambulatory pediatric neurology or developmental pediatrics clinics of the Montreal Children's Hospital for initial evaluation of a suspected developmental delay were enrolled. Features evident on history or physical examination were determined at intake as were the laboratory tests (and their rationale) requested by the evaluating physicians. Six months post initial assessment, detailed chart review was undertaken to determine if an etiology was found and the basis for such a determination. Bivariate and multivariate logistic regression was used to test for associations between factors present at intake and successful ascertainment of an underlying etiology. Two hundred and twenty-four children met study criteria. Etiologic yield varied across childhood developmental delay subtypes, and was 44/80 for global developmental delay [GDD] (55%), 13/22 for motor delay [MD] (59.1%), 3/72 for developmental language disorders [DLD] (4.2%), and 1/50 for autistic spectrum disorders [ASD] (2%). For GDD, the presence of historical features or findings on physical examination was associated with greater likelihood for successful etiologic determination with the following items significant in multiple logistic regression analysis; microcephaly, antenatal toxin exposure, focal findings. For MD, physical findings or the co-existence of a cerebral palsy symptom complex predicted a successful search for etiology. For both groups, the severity of the delay did not predict etiologic yield. For both groups, a small number of etiologic categories accounted for the majority of diagnoses made. Etiologic yield in childhood developmental delay is largely dependent on the specific developmental delay subtype. Paradigms for systematic evaluation of this common child health problem can be suggested, however they await validation.

Keywords: Etiology; Developmental delay

1. Introduction

Developmental delay is a common problem in pediatrics and a frequent prompt for referral by the primary care provider to either a pediatric neurologist or developmental pediatrician for sub-specialty evaluation [1,2]. To referring physicians, an important, if not indeed the primary aspect of this sub-specialty evaluation is the careful search for a causal explanation for the child's observed delay [3]. Searching for and determining a specific underlying etiology has important implications with reference to ongoing management related to such issues as recurrence risk estimation, accurate prognostication, mechanisms of medical follow-up and on rare occasions, specific therapeutic interventions [4]. Determining the profile of etiologies and their frequency of occurrence in a population of developmentally delayed children will have implications at a policy level with regards to issues of prevention and targeted service provision.

Theoretically, a plethora of etiologies can be responsible for childhood developmental delay. Accurate identification of etiology poses considerable challenges and may call for a large number of costly laboratory investigations. While there is controversy regarding which tests should be done, it is agreed that an all-inclusive 'shotgun' approach lacks validity and economic support at the clinical level [2–6]. There has been wide variability in reported etiologic yield reflecting differences attributable to technological advances (especially in genetics and neuroimaging), the thoroughness of evaluation and the characteristics of the original sample

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Table 1
Developmental delay subtype[a].

	GDD	DLD	ASD	Motor delay
Total number	80	72	50	22
Males	54 (67.5%)	60 (83.3%)	41(82%)	11 (50%)
Females	26 (32.5%)	12 (16.7%)	9 (18%)	11 (50%)
Age at initial parental concern (months) mean ± SD	23.5 ± 13.7	25.2 ± 8.4	24.2 ± 10.2	19.4 ± 21.2
Age at child specialty assessment (months) mean ± SD	36.2 ± 15.9	43.3 ± 9.2	40.6 ± 9.7	24.0 ± 13.7

[a] GDD, global developmental delay; DLD, developmental language disorder; ASD, autistic spectrum disorder.

[4]. Thus, uncertainty exists regarding the value of specialty evaluation for etiologic determination and the rationale for specific laboratory testing.

We wish to report a prospective study undertaken to evaluate the etiologic yield across the spectrum of early childhood developmental delay subtypes in the clinical setting of ambulatory sub-specialty evaluation. While the yield in the various categories of developmental delay subtypes has been reported recently by the authors in separate publications [7–9], bringing this data together on the disparate delay subtypes allows for the detection of trends in evaluation and yield that suggest the possible formulation of a diagnostic paradigm. Aside from profiling the etiologic yield determined, factors present on initial evaluation, and where possible, the yield of laboratory testing under varying conditions, will also be reported.

2. Methods

Subject selection and study procedures have been described in detail previously [7–9] and will be briefly summarized herein. Over an 18-month inclusive period (June 1, 1996–November 30, 1997) all children referred to either the general Pediatric Neurology or Developmental Pediatrics Ambulatory Clinics at the Montreal Children's Hospital of the McGill University Health Centre were consecutively recruited. To be enrolled in the study, a child had to be younger than 5 years of age at the time of initial specialty assessment of a suspected developmental delay. Children were excluded from study entry if they had undergone a prior specialty assessment (i.e. if the current referral was for a second opinion). They were also excluded from subsequent data analysis if a developmental delay was not confirmed subsequent to specialty assessment or if the child/family failed to attend all requested diagnostic investigations selected by the evaluating specialty physician.

This study did not put in place a specific mandatory assessment strategy or testing protocol. Individual specialty physicians in the participating clinics (four pediatric neurologists, two developmental pediatricians) carried out their own independent history and physical examination and selected, at their own discretion, specific laboratory testing on an individualized case-by-case basis. Standardized data sheets were completed at the time of initial assessment that provided demographic and referral information on each subject, as well as documenting laboratory testing ordered and the physician's specific rationale for selecting a particular laboratory test (i.e. clinically indicated or screening basis).

Six months following the initial specialty evaluation, the medical records of all participating subjects were systematically reviewed by a single investigator (MS). Based on a review of the initial specialty physician evaluation and ancillary evaluations carried out by rehabilitation professionals, each subject was assigned to a category of early childhood developmental delay according to the definitions provided below (Appendix A) and a priori decision rules. Severity of the observed delay was stratified into mild, moderate and severe categories according to the percentage of functional age compared to chronological age (i.e. mild 67–100%, moderate 33–66%, severe <33%). Inter-rater reliability of the investigator assignment of a category of delay and attached severity was established through a second independent assignment by a second investigator (AM) on a random sample of subjects. In addition, at the time of this 6-month post-assessment chart review, pertinent clinical features on history or physical examination, the results of recommended testing, etiologic determination (if any), type of etiology determined and possible etiologic impact (i.e. modification of recurrence risk, medical management or treatment) were identified. For the purposes of this study etiology was defined according to the standard of Schaefer and Bodensteiner as: 'a specific diagnosis that can be translated into useful clinical information for the family, including providing information about prognosis, recurrence risk and preferred modes of available therapy' [5].

From the data obtained, descriptive statistics on the various populations of interest (i.e. developmental delay subtypes) were generated. Bivariate associations between individual variables evident at the initial intake and determination of etiology were explored either by chi-square or Fisher exact tests, as appropriate. For subtypes with a sufficient number of successful etiologic determinations (i.e. global developmental delay subtype) a multiple logistic regression analysis with etiology determination (yes/no) as the dependent variable and clinical features as independent variables were carried out. For all hypotheses tested, a significance level of 0.05 was selected.

Table 2
Developmental delay subtype[a].

	GDD		DLD		ASD		Motor delay	
Total number	80		72		50		22	
	Number done	Number positive	Number done	Number positive	Number done	Number positive	Number done	Number positive
Metabolic studies								
Screening	12	0	2	0	11	0	6	0
Indication	9	0	1	0	3	0	3	0
Genetic studies								
Screening	25	2	12	0	31	0	3	0
Indication	30	3	9	0	11	0	2	0
EEG								
Screening	44	0	37	0	34	1	N/A	
Indication	0	0	0	0	0	0		
Imaging								
Screening	24	5	27	0	28	0	2	0
Indication	32	14	6	0	5	0	10	7
Overall etiologic yield (%)	44 (55%)		3 (4.1%)		1 (2%)		13 (59.1%)	

[a] GDD, global developmental delay; DLD, developmental language disorder; ASD, autistic spectrum disorder.

Table 3
Developmental delay subtype[a]

	GDD	DLD	ASD	Motor delay
Total	80	72	50	22
Etiology determined	44	3	1	13
Etiologies determined (#)	Cerebral dysgenesis (10) HIE (9) Toxin exposure (9) Chromosomal abnormalities (6) Psychosocial neglect (3) Neuromuscular disorder (2) Genetic syndromes (2) Other (3)[b]	Hearing loss (2) Opitz syndrome (1)	Landau–Kleffner	HIE (5) Cerebral dysgenesis (2) Benign congenital hypotonia (2) Other (4)[c]

[a] GDD, global developmental delay; DLD, developmental language disorder; ASD, autistic spectrum disorder.
[b] One each of sequelae of infection, leukodystrophy, multiple sensory impairments.
[c] One each of toxins, myelodysplasia, autosomal recessive spastic ataxia of Charlevoix–Saguenay, brachial plexus palsy.

This study's protocol was reviewed and approved by the Montreal Children's Hospital hospital's Institutional Review Board. Informed written consent to their child's participation in the study was obtained from the parents or guardians prior to study entry.

3. Results

In all 258 children were referred to the participating clinics for initial evaluation of a suspected developmental delay during the enrollment period. Thirty-four children were excluded from subsequent data analysis: 20 in whom suspected developmental delay was not confirmed upon specialty evaluation, and an additional 14 for non-compliance (i.e. the families did not attend all physician-requested laboratory investigations). The type of childhood developmental delay documented together with associated gender distribution, mean age at initial parental concern and mean age at initial specialty assessment for this cohort are listed in Table 1. For each category of developmental delay, the number of children undergoing specific laboratory testing, the rationale for test selection (i.e. screening or clinically indicated), testing yield and overall etiologic yield subsequent to completion of specialty history, physical examination and laboratory testing are presented in Table 2. It is important to note that etiologic yields amongst the categories were sharply divergent: either exceeding 50% (i.e. global developmental delay - 55%, motor delay - 59.1%) or less than 5% (i.e. developmental language disorder - 4.1%, autistic spectrum disorder - 2%). The etiologies determined and their frequency according to the specific category of developmental delay are listed in Table 3.

Where etiologic yield was sufficient (i.e. global developmental delay and motor delay) bivariate associations were assessed between possible predictor variables, laboratory testing and eventual etiologic determination. The results of the bivariate association analysis are presented in Tables 4 and 5. For global developmental delay, the presence of historical features (e.g. a family history, consanguinity, intrapartum or neonatal complications, developmental regression, or toxin exposure) and physical findings (e.g.

Table 4
Global developmental delay subtype bivariate associations.

	Etiology determined		*P*-value (Chi-square analysis)[b]
	Yes	No	
Gender			
Male (54)	29	25	0.7370
Female (26)	15	11	
Historical features			
Present (32)	24	8	0.0033[a]
Absent (48)	20	28	
Physical findings			
Present (46)	35	11	< 0.0001[a]
Absent (34)	9	25	
Microcephaly			
Present (15)	14	1	0.0010[a,b]
Absent (65)	30	35	
Dysmorphology			
Present (23)	15	8	0.2433
Absent (57)	29	28	
Focal findings			
Present (16)	14	2	0.0043[a,b]
Absent (64)	30	34	
Genetic testing			
Screening (25)	2	23	> 0.9999[b]
Indicated (30)	3	27	
Neuroimaging			
Screening (24)	5	19	0.0924[b]
Indicated (32)	14	18	

[a] Significant at 0.05 level.
[b] A Fisher Exact test was used to test for this association.

Table 5
Motor delay subtype bivariate association

	Etiology determined		*P*-value (Fisher exact test)[a]
	Yes	No	
Gender			
Male (11)	5	6	0.3870
Female (11)	8	3	
Historical features			
Present (14)	10	4	0.1870
Absent (8)	3	5	
Physical findings			
Present (17)	13	4	0.0048[a]
Absent (5)	0	5	
Severity			
Mild (14)	7	7	0.3802
Moderate (8)	6	2	
Cerebral palsy			
Present (6)	6	0	0.0461[a]
Absent (16)	7	9	

[a] Significant at 0.05 level.

macrocephaly, microcephaly, dysmorphology or focal abnormalities) were predictive of eventual etiologic determination. Stratified according to severity, 25 of 42 children (59.5%) with mild delay, 15 of 34 children (44.1%) with moderate delay and all four children with severe delay had an etiology determined. Thus increasing severity was not systematically associated with a higher etiologic yield. Multiple logistic regression analysis including all previously identified predictor variables identified the following variables as statistically significant independent predictors of successful etiologic determination: (1) microcephaly, (2) historical features, (3) toxin exposure, and (4) focal findings.

For children with global developmental delay, the yield on cytogenetic testing whether done on a clinically indicated (i.e. dysmorphology) or screening basis, was not significantly different. This was in distinction to the yield from neuroimaging which when done on an indicated basis was twice as likely to have a diagnostic yield than when done on a screening basis. This very closely approached the threshold of statistical significance ($P = 0.092$).

The relative contribution of the history, physical examination and laboratory investigation to etiologic determination in children with global developmental delay is presented in Fig. 1. In nine of 44 (20.5%) instances in which an etiology was determined in this category, laboratory testing was the sole means of so doing. Similarly in 17 of 44 cases (38.6%), history and/or physical examination alone were sufficient to determine eventual etiology.

For the category of motor delay, the presence of physical findings or a concomitant diagnosis of a cerebral palsy symptom complex was found to be highly predictive of etiologic determination, whereas the presence of historical features was not. Severity of the observed delay in this

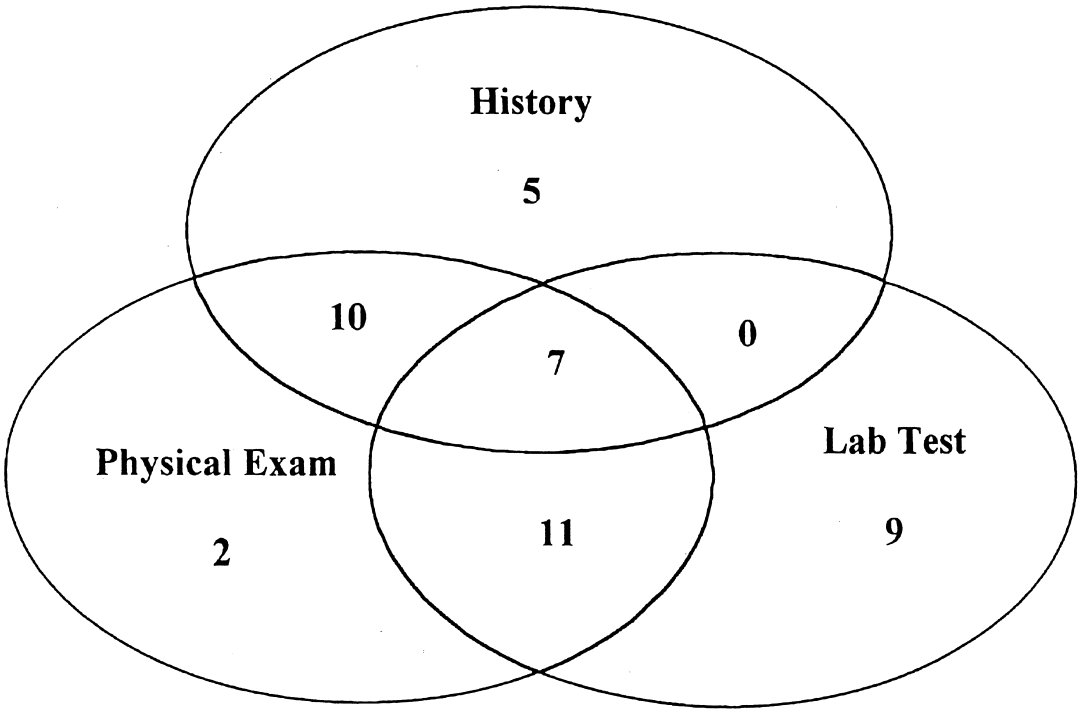

Fig. 1. Venn diagram depicting relative contribution of history, physical examination and laboratory testing to determining etiology in the 44 cases of children with global developmental delay for whom an etiology was determined.

group was also not found to be predictive of eventual etiologic yield.

In 15 of 44 cases (34.1%) in which a child with global developmental delay had an etiology determined there was an impact of such a determination apparent on either the estimation of recurrence risk, medical management or therapeutic intervention. This was so in eight of 13 cases with motor delay, two of three cases with developmental language disorder and in the sole case of an autistic spectrum disorder with an etiology determined. It is interesting to note that for those with global developmental delay and an etiology determined, almost half (21 of 44) had a theoretically preventable etiology (hypoxic ischemic encephalopathy, antenatal toxins, psychosocial neglect). This was so in slightly more than half (seven of 13 cases) of those with motor delay and an etiology determined (hypoxic ischemic encephalopathy, antenatal toxins, brachial plexus palsy).

4. Discussion

Our study sample is felt to be reasonably representative of the local community of children with developmental delay for a variety of reasons. Universal health insurance coverage in Quebec (Medicare) removes any potential economic or third party barriers to specialty medical care provision. A prior survey of our local physician referral network indicates that almost three-quarters (72%) of these physicians refer all or most of the children in their practice with developmental delay for hospital-based sub-specialty evaluation [10]. Furthermore the majority of children in each developmental delay subtype in which severity could be assessed were found to have either mild or moderate delay (i.e. 95% of global developmental delay, 98.2% of developmental language disorder and all with an isolated motor delay). Finally the study did not utilize, as sites for subject recruitment any specialty clinics in which pediatric neurology services were provided that might have inflated the estimation of etiologic yield (e.g. neonatal neurology and neurogenetic clinics). General pediatric neurology or developmental pediatric ambulatory clinic receiving community-based referrals were the sole sites of subject recruitment for the study.

From our results, it is readily apparent that a sharp dichotomy exists with respect to etiologic yield depending on the specific childhood developmental delay subtype under study. For those children with either a global developmental delay or an isolated motor delay, an etiology was determined subsequent to history, physical examination laboratory testing in slightly more than half of instances (55 and 59.1%, respectively). Conversely, for those children with either developmental language disorder or an autistic spectrum disorder, an etiology was rarely identified (4.2 and 2%, respectively). This sharp distinction suggests that the initial point in a developmental delay evaluation paradigm should be the accurate characterization of a child's specific developmental delay subtype. It is this ascertainment that should direct physician and family expectations of determining an etiology and to some extent the selection of specific laboratory testing to be undertaken.

Our yield of 55% in children with global developmental delay replicates the result of a retrospective study conducted in our institution applied to a single pediatric neurology practice [10]. It is consistent with other more recent community-based studies [11,12]. It is however substantially greater than studies from the 1980's [13–16], perhaps reflecting recent advances in genetic and neuroimaging technologies. It is however more than twice the yield found in a recent sample derived from community-wide educational institutions in metropolitan Atlanta [17]. This difference can be attributed largely to the benefits of systematic sub-specialty evaluations that were not part of the Atlanta study. As for our yield with respect to either single domain developmental delay (i.e. motor delay or developmental language disorder) or the autistic spectrum disorders, comparable prospective community-based studies are absent from the medical literature.

As highlighted in Table 2, laboratory testing for children in the delay subtypes was selectively undertaken. However with the exception of genetic and imaging studies in children with global developmental delay and imaging studies in those with an isolated motor delay, such studies were largely done on a screening basis as opposed to a clinically indicated basis. For those two subtypes in which an etiology was more often than not determined, a small number of categories was responsible for the bulk of diagnoses made. In children with global developmental delay, the categories of cerebral dysgenesis, hypoxic-ischemic encephalopathy, antenatal toxin exposure and chromosomal anomalies provided 34 of 44 (77.2%) diagnoses ultimately made. For those with motor delay, the categories of hypoxic-ischemic encephalopathy, cerebral dysgenesis and benign congenital hypotonia accounted for nine of 13 (69.2%) diagnoses made.

For both global developmental delay and motor delay subtypes, approximately half of identified etiologies were theoretically preventable (47.7% of global developmental delay, 53.8% of motor delay). This suggests possible targets for prevention strategies to minimize acquired disability. Furthermore in a significant proportion of those in which an etiology was determined in both of these subtypes (34.1% for global developmental delay, 61.5% for isolated motor delay) an impact upon medical management in the domains of recurrence risk estimation, medical follow-up or therapy offered was apparent. This observation additionally highlights the value of a careful causal search.

The low etiologic yield in the autistic spectrum disorders and developmental language disorder subtype is both disappointing and frustrating. It serves tangibly to demonstrate our present relative lack of understanding of mechanisms affecting the brain that results in predominantly speech and

language impairment, either in a quantitative or a qualitative manner. This small yield should serve to challenge us to adapt, utilize and apply to this population newer innovative technologies (e.g. functional imaging) that may provide the possibility of advancing our mechanistic understanding of these delay subtypes. While the yield is indeed low in both groups, in three of four cases where an etiology was identified (i.e. hearing loss, Landau–Kleffner variant), specific therapeutic intervention implications were apparent (i.e. hearing amplification, anticonvulsants) that modified eventual outcome. Finally, especially with reference to children with autistic spectrum disorders, specialty evaluation is often the means of initial diagnosis of this entity that is frequently not accurately diagnosed in the community [1,18].

In children with global developmental delay, the frequency of etiologic determination permits the identification of predictor variables evident on history and examination at the time of initial specialty evaluation, suggesting that the search for an etiology will indeed be successful. These variables include collective documentation of specific historical features (i.e. antenatal toxin exposure) and physical findings (i.e. abnormalities in head circumference, dysmorphic features, focal findings). Bivariate associations and further multiple logistic regression analysis revealed that antenatal toxin exposure, microcephaly and focal findings retained their significance as independent predictor variables in this population. Thus their documentation at the time of initial assessment should invigorate an etiologic search. For children with an isolated motor delay, physical findings (i.e. objective weakness, tone and reflex changes, asymmetric movements) and the symptom complex of an associated cerebral palsy serve a similar function. It is interesting to note that in both subtypes, increasing severity of observed delay did not impact significantly on etiologic yield.

While our study was not designed to assess the cost-benefit ratios of specific laboratory testing in certain clinical situations, some observations can be made. For children with the developmental language disorder and autistic spectrum disorder developmental subtypes, prospective studies with large numbers of subjects will be necessary to address the issue of screening these children with modalities such as genetic testing (karyotype, FMR-1, molecular genotyping), EEG and imaging that have an apparent low yield (less than 5%). In all types of developmental delay, metabolic testing is usually done on a screening basis with little apparent yield. Although individual metabolic disorders are rare, their considerable genetic/therapeutic implications mandates diagnostic vigilance. Thus specific testing for these disorders would likely best be left for situations raising a diagnostic suspicion such as positive family history, parental consanguinity, developmental regression or, episodes of acute decompensation.

For children with global developmental delay, genetic testing (i.e. karyotype, FMR-1, molecular genotype) did not have a different yield for those with a clinical indication (usually observed dysmorphology) or when done a screening basis. While neuroimaging on a clinically indicated basis was twice as likely (43.7 vs. 20.8%) as on a screening basis to be informative, this approached but did not cross the threshold of statistical significance ($P = 0.092$) which may partly reflect limited statistical power of our analysis. The value of these tests on a screening basis alone however cannot be underestimated as seven of 44 diagnoses made in this subtype as a whole (15.9%) were as a result of genetic and imaging testing carried out without prior indication. For the majority of our subjects, the local factor of imaging accessibility meant that the primary modality utilized was computed tomography rather than the more refined magnetic resonance imaging. Thus our yield on imaging studies is likely to be an underestimate of actual subtle pathology that is beyond the resolving (i.e. diagnostic) power of computed tomography.

Our results suggest the framework of an evaluation paradigm for childhood developmental delay. The first essential step is to accurately characterize the developmental delay subtype. For those with global developmental delay in addition to a detailed history and physical examination, genetic testing (karyotype and FMR-1) and imaging (MRI preferable) should be undertaken on either a screening or clinically indicated basis. From the perspective of etiologic determination, additional laboratory testing should be directed by the findings on history and physical examination. For isolated motor delay, specific laboratory testing should be directed by findings on physical examination: evidence of a central process leads to imaging, while that of a peripheral process to electromyography/nerve conduction studies. In developmental language disorders, only audiometry may be recommended on a screening basis. For those children with an autistic spectrum disorder, recurrence risk implications and therapeutic implications respectively suggest serious consideration of genetic testing (karyotype, FMR-1) and electroencephalography. This framework awaits prospective validation. It can also be considered applicable with confidence to a population similar in socio-economic and ethnic profile to that from which the study population was drawn.

It must also be remembered that etiologic determination, while important and the focus of this report, is but one aspect of the specialty evaluation of the young child with developmental delay [4]. Additional equally important facets of this evaluation are referral to appropriate local rehabilitation resources, family counselling and management of any associated medical conditions (e.g. epilepsy, spasticity, sleep and behavioral disorders). Successful management of these and other relevant issues such as prognosis or recurrence risk estimation is to some extent predicated on an accurate etiologic determination, if possible. Thus classification of a child's delay (especially in cases of a global developmental delay or motor delay subtype) is not an end-point but rather a prompt for a careful causal search.

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Appendix A.

Global developmental delay was defined as a significant delay in two or more developmental domains (gross/fine motor, cognition, speech/language, personal/social, or activities of daily living).

Motor delay was defined as a significant delay in gross and/or fine motor skills with preservation of age appropriate performance in other developmental domains.

Developmental language disorders were defined as a significant delay restricted to speech and language skills with normal performance in other developmental domains.

Autistic spectrum disorders were defined as having core features of observed qualitative deficits in social skills, communication (verbal and non-verbal), and restrictive/repetitive patterns of behavior.

Significant was defined as two or more standard deviations below the mean on norm referenced developmental screening or assessment tests.

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