

DOI: 10.21767/2472-1964.100008

“Common Developmental Delay” in Full-term Children: A Common Neurological Profile to Aid in Clinical Diagnosis

Gupta SN¹, Gupta VS² and Ahmed A³

- 1 Pediatric Neurology, CAMC, 205 Grandview PT. Dunbar, USA
- 2 Texila American University, Woolford Ave, Georgetown, Guyana, USA
- 3 Section of Child Neurology, Department of Pediatrics, West Virginia School of Medicine (Charleston Campus) West Virginia, USA

Abstract

Depending on the course, developmental disorders can be divided into three groups. In clinical practice of child neurology, developmental delay of unknown etiology without regression is probably the most common group. To date, no reports have described commonly encountered developmental delay in full-term children.

Based on what is known and longitudinal clinical observation, in this review, we propose and describe a common neurological profile in a homogenous population of children with “common developmental delay”.

In authors’ view, adherence to the proposed profile will (1) Identify common developmental delay, (2) Differentiate it from other treatable conditions, (3) Optimize the need for laboratory investigation, (4) Facilitate clinical interventions in timely manner, (5) Avoid a legal implication of delay in management, and (6) Allow to define the developmental status of subjects for clinical research.

Future studies should analyze prospectively the diagnostic significance of the proposed common neurological profile in full-term children with “common developmental delay”.

Keywords: Developmental delay; Common developmental delay; Regression; Etiology; Seizure; Behavioral problem; Learning disability

Corresponding author: Gupta SN

✉ suryangupta@rediffmail.com

Pediatric Neurology, CAMC, 205 Grandview PT. Dunbar, USA.

Tel: 3045451975

Citation: Gupta SN, Gupta VS, Ahmed A. “Common Developmental Delay” in Full-term Children: A Common Neurological Profile to Aid in Clinical Diagnosis. *J Clin Dev Biol.* 2016, 1:2.

Received: February 23, 2016; **Accepted:** March 04, 2016; **Published:** March 09, 2016

Introduction

Clinical suspicion of delay in developmental milestones is assessed in domains of motor development, verbal and non-verbal languages, learning in class-setting, and social interaction [1]. Global developmental delay is defined by a delay in 2 or more domains of developmental milestones [2, 3].

The spectrum of developmental impairments are subject to pathophysiological variations. Developmentally affected children, at the very least, have a learning disability. Neurologically, there are three main reasons to evaluate developmental delays: (1) To identify a treatable condition or etiology, (2) To institute an early intervention, (3) To expect and manage future comorbidities, and (4) To identify those parents who will need genetic counseling.

Based on what is known and longitudinal clinical observation, we propose and describe a common neurological profile in children with common developmental delay to aid in clinical diagnosis.

Notably, children with common developmental delay are born at full-term gestation. They have no adverse perinatal events such as maternal–fetal infection, fetal alcohol syndrome, or cerebral malformations. They are medically in good health and are intellectual normal. Interestingly, their developmental milestones do not regress, rather their developmental milestones improves overtime.

Method

Literature search

An exhaustive review of published literature was undertaken using the electronic databases PubMed, Embase, OVID Medline, Global Health, WHO-LIS and WHO regional databases. Different combinations of the terms “developmental delay”, “neurodevelopmental delay”, “comorbid” (comorbid, comorbidity, comorbidities), “ADHD”, “epilepsy” (epilepsy, epilepsies, epileptic), “seizure”, “neuropsychiatric”, “associate”

(association, associated), “behavior” (behavior, behavioral), “disorder” with appropriate variations were used. Terms were slightly modified where necessary to fit the search terms offered in the respective databases. Final searches on all databases were undertaken on November 30, 2014. Reference lists of all selected articles were additionally screened.

Inclusion and exclusion criteria

Comorbidities were defined as any other medical conditions coexisting in addition to developmental delay. All articles linking developmental delay of unknown etiology without regression to co-existing medical conditions (“comorbidities”) were included. Any articles involving developmental delay with regression or of known etiology (including ischemic injury at birth) were excluded. All studies examining specific population subsets such as very low birth weight or extremely premature neonates were excluded.

Results

The phrase “developmental delay” or “neurodevelopmental delay” alone produced 7689 articles. In combination with other terms, the largest number of results with any search was 4972. A total of 24 studies met inclusion criteria (**Table 1**). The terms “Neurodevelopmental delay without regression”, “developmental delay without regression” and “developmental delay of unknown etiology” did not produce any results with any combination.

Past Reports of Developmental Delay

No studies were reported from a pediatric neurology setting and no studies were carried out exclusively in children with “common developmental delay”.

Table 1 summarizes what is known from those studies that imply children as common developmental disorder [4-6].

Table 1 Summarizes what is known from those studies that imply children as “common developmental disorder” [4-16].

DD: Developmental Delay

^aBased on DSM-IV-TR four criterion, all children had poor motor coordination substantially below expected (criteria A). Functional impairment in daily life or in academic achievement (criteria B). No known etiology (criteria C). Finally (criteria D), all children were typically achieving on intelligence (IQ equal or above 80) measured with the short version of the Wechsler Intelligence Scale for Children.

Study Type [Reference]	Country / Clinical Setting / Subject Type	Study Objective / How developmental delay was defined in the study / Comment
Prospective [4]	India / Pediatrics / DD with and without microcephaly	To study the profile of children with developmental delay and microcephaly / Developmental delay in two or more fields below two standard deviation and Development Quotient / Intelligent Quotient of < 70 were classified as developmental delay and mental retardation, respectively.
Case-control [5]	Belgium / Psychology / Developmental coordination disorder	Investigate the mathematical problems in children with various degrees of developmental coordination disorder/Based on DSM-IV-TR four criterion ^a [6, 7] / “DD of other etiology” was not defined. This included DD of known etiology with or without regression
Retrospective case-control study [8]	USA / Teaching Research Institute / Autism, normal and other DD	To validate a parent-caregiver measure of comorbid symptoms in autism, for the Sense and Self-Regulation / Presence of clinical hypertonia or hypotonia with motor delay / Included 15 children with cerebral palsy and 10 children with Down syndrome.
Case-control [9]	USA / National Center on Birth Defects and Developmental Disabilities / developmental disabilities	To assess the prevalence of medical conditions, health care use measures, health impact measures, and selected indicators for unmet health needs / Health professional reports of developmental status / DDs was divided into 1. Autism 2. Intellectual disability without #1, (3) ADHD without #1 and 2 and 4. Learning disability without # 1, 2 and 3.
Case control [10]	USA / Psychology / Developmental delay	To assess for clinical diagnosis of ADHD using a structured interview / Bayley Scales of Infant Development [11] / All DD were ambulatory had a moderate to borderline range of cognitive delay without autism.
Retrospective [12]	Hong Kong / Child Assessment Service / Mental retardation and developmental delay	To report the clinical profile of children with mental retardation and developmental delay diagnosed by the Child Assessment Service / No information was available.
Retrospective [13]	Australia / Pediatrics / Developmental disabilities	To determine the prevalence of overweight and obesity in children with developmental disabilities attending a metropolitan Diagnosis and Assessment Service / Griffiths Mental and Developmental Scale [14]
Retrospective case control [15]	Italy / Neurological and Psychiatric Sciences / Autism	Compare sensorimotor development in children with autism with that of developmental delay and to verify developmental unevenness profiles through correlations amongst domains and chronological age / Both autism and developmental delay were defined based on DSM-IV criteria , clinical observation, and an agreement between two child psychiatrist.
Population-based [16] Survey	Australia / Speech Pathology and audiology / Speech disorders	To report prevalence, comorbidity and socioeconomic status of children with speech disorders / Speech disorders were record based on the reports of difficulty talking, producing speech sounds, or stuttering.

General Consideration

Children with common developmental delay are generally unrecognized in general population. When seen in acute neurological setting, their developmental status is likely to be overlooked.

Terminology

Currently, no uniform term is in use to express children with developmental delay who are seen on a daily basis in child neurology clinics. Previous studies have used several different terms such as “non specific” or “routine” developmental delay, “developmental coordination disorder”, “developmental delay with no specific diagnosis”, and simply “developmental delay” [10]. The term has been intermixed with the classification, domain of developmental disability, severity, and comorbidities [12-17].

Recently, the term “Mental retardation” has been replaced by “Intellectual disability”.

Children with “common developmental delay” may have a learning disability, but they are not intellectual disable. In this clinical review, we coined the term “common developmental delay” to express a homogenous group of full-term children with “developmental delay of unknown etiology without regression”. The use of this new term collectively provides: (1) A clinically based common diagnosis, (2) Differentiates it from other groups of developmental delay which may require further investigation, (3) Most importantly, the proposed term separates the diagnosis from other aspects of developmental delay such as the domains of disability and comorbidity.

Arguably, the term “common developmental delay” can be seen as unfocused and a label of exclusion.

Classification

The literatures have placed emphasis on the classification of developmental disability domain rather than the spectrum of developmental disorder. Most classification systems have focused on specific etiologies or impairments such as motor impairment in cerebral palsy, intelligence quotient (IQ) less than 70 in intellectual disability, and interpersonal or societal interaction impairment in autism.

A study of developmental delay was classified into the following subgroups: (1) Genetic syndromes with recognized etiology, (2) Global developmental delay / intellectual disability in association with dysmorphic features, but unknown etiology, (3) Global developmental delay / intellectual disability without dysmorphic features, (4) Recognized etiology, brain malformations, inborn errors of metabolism, leukoencephalopathies, epileptic syndromes and (5) Developmental language impairment, and neuromuscular disorders. Furthermore, 74 / 241 (31%) children with adverse events after preterm or at term delivery were classified into subgroups such as cerebral palsy and disabilities without cerebral palsy [18]. Fenichel’s text book of clinical pediatric neurology used the term “Psychomotor retardation” as equivalent to developmental delay. The author distinguished this from “Psychomotor regression” [19].

Table 2 Lists a simple classification system of the entire clinical spectrum of developmental disorders based on their developmental course and etiology.

MELAS: Mitochondrial Encephalomyopathy Lactic acidosis and Stroke-Like Episode

Foot note: Developmental delays are a heterogenous group of disorders. While specific developmental disorder (Group III) remains the primary concern, it is Group I is commonly encountered in daily practice of developmental neuropsychiatrics

Group I	Group II	Group III
No developmental regression of known or of unknown etiology	Questionable developmental regression of known or of unknown etiology	With developmental regression of known or of unknown etiology
Etiologically Based Clinical Condition		
Perinatal adverse events, Autism spectrum disorder, Non-dysmorphic genetic disorder, Common developmental delay	Cerebral palsy-like syndromes; Arginase deficiency, Mucopolidosis type IV, Congenital myasthenia gravis	Neurodegenerative disorders of grey matter, white matter, and combination of both; Rett syndrome, Adrenoleukodystrophy, MELAS

Contrary to the statement that “Given the complexity of neurodevelopmental disabilities, it is unlikely that a single classification system will fit all needs” [20], **Table 2** lists a simple classification system for the entire clinical spectrum of developmental disorders based on their developmental course and etiology.

The subject of this review, “Common Developmental Delay” is the most common amongst Group I. These children are born full-term, are in good health, and have no intellectual disability. They do not regress, rather improve in their already acquired developmental milestones and cause is unknown.

Prevalence

In general , developmental disorders occur in 2% to 3% of all children [21].

The actual prevalence of common developmental delay in children is unknown. However, its daily encounter in child neurology practice can attest to its common occurrence.

In search for etiology and degree of intellectual disability in 241 children, a recent study identified etiology in 66.4%. A genetic diagnosis was made in 19.5%. More importantly, 167 / 241 (69%) of children with disability had no prenatal, perinatal, and neonatal adverse events [18].

Etiology

The etiology of common developmental delay in full-term children is unknown. It presumably has genetic or idiopathic etiology. The acceptance level of common developmental delay as a diagnosis is low. However, common migraine in the same etiological profile is a well accepted neurological diagnosis.

Common Neurological Profile

A common neurological profile to aid in a clinical diagnosis of common developmental delay is shown in **Table 3**.

Table 3 Lists common neurological profile for full-term children with developmental delay of unknown etiology without regression. CBC: Complete Blood Counts; CMP: Comprehensive Metabolic Panel; MRI: Magnetic Resonance Imaging

	Clinical Characteristics
Presentation	For developmental assessment, new onset seizure, behavior problem, learning disability. Suspicion of early closure of anterior fontanel, inattention, Rarely, presents with torticollis with and without deformational plagiocephaly during infancy and movement or gait abnormality in later childhood
Age and Sex	Younger the age of onset of 2 or more domains of developmental delay severe is outcome. Both genders are affected
Developmental Status and the Course	Mother is the first one to recognize that the child has not been acquiring age appropriate Expected developmental milestones. No history of developmental regression, rather the child has been improving
Medical History	Frequent choking, sleep disturbance, chronic constipation, and an increased need for medical care during infancy
Birth history	Children are born full-term normal spontaneous vaginal delivery. Often, a history of umbilical cord wrapped around the neck is obtained.
Family History	No family history of developmental delay, consanguinity, and mother had no recurrent miscarriages
Examination: General	Normal appearance, normocephalic, good eye contact, verbal, ambulatory, and friendly. Visual and hearing function is normal in children with common developmental delay. No associated organomegaly or congenital abnormalities
Neurological	Some may have facial indifference, deformational plagiocephaly, fixed torticollis, strabismus, or cortical motor deficit. Fine motor movements are slow. They have tendency to walk on the toes and inability to walk on the heels. Muscle tones are generally normal. Deep tendon reflexes are normal or hyperactive.
Differential Diagnosis	Cerebral palsy-like syndromes, Non-dysmorphic genetic disorders, and Medical- and Neuro-genetic disorders
Laboratory	CBC, CMP, thyroid dysfunction, Lead level, Inborn errors of metabolism, and Fragile X DNA analysis are all normal. Chromosomal array and brain MRI in some reveal abnormality of unknown significance.
Comorbidity	Includes behavioral problem, seizure disorder, and a learning disability in the classroom-setting
Management	Reassurance, an early intervention and late intervention such as supportive learning, and symptomatic therapy for emergence of associated comorbidities such as seizure or behavioral problems

Arguably, the proposed “common neurologic profile” can be seen as a common core problem shared by other developmental disorders and the symptomatology in isolation may seem to have no relationships.

Conditions Mimicking Common Developmental Delay

Static encephalopathy

In the past, the term “static encephalopathy” has been used to imply a single adverse insult with no regression of an acquired developmental delay, which occurs during prenatal period such as fetal alcohol asyndrome [22] or postnatal period such as acute bacterial meningitis [23], herpes encephalitis [24], or shaken baby syndrome [25].

The static encephalopathy of childhood is not always a static condition. An X-linked dominant neurodegenerative disorder of iron accumulation of the brain, mimics static encephalopathy, which can regress in adulthood [26]. This is rare condition, which does not negate the general principle.

Primary autism spectrum disorder

Kanner was first to recognize the lack of affective component along with other signs and symptoms of developmental delay in children with autistic spectrum disorder [27].

DSM V that was published in 2013 defines autistic disorder as a

qualitative impairment in social interaction and communication with restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. Symptoms must be present during developmental years. The criteria no longer include delays in language. In autism spectrum disorder, a specific cause can be found in a limited (10% to 30%) number of patients [28].

An additional domain of impair social interaction to common developmental delay profile characterizes primary autistic spectrum disorders [29]. Unlike autism, children with common developmental delay have an even sensorimotor profile.

Non-dysmorphic genetic disorders

The genetic syndrome is generally recognized by the presence of dysmorphic features [30].

However, genetic syndromes with no dysmorphism caused by microdeletion mimics common developmental delay, which can be differentiated by an abnormal chromosomal microarray.

About 20% to 30% of children with developmental delay with no obvious dysmorphic features have abnormal microarray DNA analyses. The importance of such genetic abnormality largely remains unknown.

Cerebral palsy

The question is where cerebral palsy fits in the spectrum of developmental delay. Cerebral palsy is characterized by motor deficits, abnormal movement, and abnormal posture [31]. The

motor deficits include hemiparesis, paraparesis, quadriplegia, or movement disorders. In practice, cerebral palsy is almost always associated with common neurological profile of common developmental delay.

Cerebral palsy-like syndromes should be considered in the presence of specific neurological signs, such as specific movements or in the absence of intellectual disability. If the described common neurological profile is followed closely, it is very unlikely that a neurodegenerative hereditary condition will be overlooked.

Alternative Conditions Suspected in Common Developmental Delay

Some of the clinical conditions that are frequently suspected in children with common developmental delay are: (1) Early fusion of anterior fontanel or hearing abnormality during infancy, (2) Absence seizure of childhood secondary to infrequent staring, (3) Acute onset of movements mimicking partial motor seizure, and (4) Gait difficulty later in childhood. Some of these children diagnosed as “High-functioning autism”.

Episodes of specific movements such as choreoathetosis or non-specific variable movements suggesting motor seizure are not uncommon in children with common developmental delay. Occurrence of these movements should not be seen as a regressive symptom.

Arguably, there are several conditions like neurofibromatosis or tuberous sclerosis which are associated with developmental delay, but they are primarily brought primarily for evaluation other than developmental delay [32].

Clinical Assessment and Challenge

Previous literatures’ focus for neurodevelopmental assessment has been separate from common developmental delay. On other hand, physicians are often untrained for evaluating childrens’ IQ or genetic condition. There is a limited availability of trained neuropsychologists and medical geneticists. Even when they are available, costly genetic testing or unavailability of a particular test in particular geographical areas of the world limits their utilization.

Several methods of developmental assesment in different age groups of children have been used. Their sensitivity and specificity have been questioned [33].

Developmental delay in a single domain of development is rare. Detection of a motor developmental delay during early infancy presents another challenge. Delay in smile, lack of visual fixation and tracking, inability to turn from back to belly and vice versa , are all useful clinical clues for identifying developmental delay. An early preference of the arm for reaching out for an object or of the leg during crawling at before age 2 years suggest likely ipsilateral focal brain lesion.

The diagnosis of common developmental delay is based on clinical history and examination. For some, common developmental delay as a diagnostic entity may be unacceptable. Frequently, parents state that the child has “no definite diagnosis”. In this

situation, a symptom as a diagnosis with unknown etiology, is not limited to common developmental delay, it is commonly used in seizure disorder.

The history

Neurologically, once the child is brought for a developmental delay concern, a delayed developmental status should be assumed unless the evaluation suggests otherwise. It is unlikely that a developmentally normal child’s developmental status is of parental concern.

The first step is to explore and confirm the reasons behind parentals’ observation. Expected developmental milestones such as physical and mental abilities and child interactions should be evaluated. This step along with the standard tools will identify the domain and severity of the delay.

The second step is to assess the past developmental course. By asking if the child is now doing better or worse. The answer in children with common developmental delay is always, “The child is doing better”. The improvement in development domains should be documented. If the developmental course is uncertain and there is no urgency, a clinical follow up should take precedence over embarking on laboratory testing.

Amongst all domains, speech delay is probably the most commonly affected developmental domain, which occurs in isolation or in combination. Often, this is erroneously attributed to otitis media or the child being bilingual [34].

A new onset true seizure is the common presentation of children with common developmental delay who were unidentified previously. The third group of children presents after the manifestation of associated comorbidities. Infrequently, some parents seek neurological evaluation concerning the child’s quality of motor movement or performance, rather than the actual delays. These are clumsiness and awkward body or hand posturing during running or writing, respectively. Rarely, they present for assessment of persistent toe walking.

A history of frequent gagging, choking, and chronic constipation are commonly obtained in clinical practice. Particularly, the sleep disturbance has been reported in the literature [35]. The presence of such symptoms are non-specific but probably represents the entire spectrum of developmental disorders.

It should be noted that common developmental delay is characterized by a lack of specific medical, genetical, or neurological feature. A history deviant from proposed common neurological profile even in the absence of developmental regression should be a red flag for evaluation for a neurodegenerative disorder.

The examination

Examination by active observation plays a pivotal role particularly when an independent objective opinion regarding the developmental status of a child is confronted. A child’s quality of spontaneous motor and speech interactions is observed. Clinical motor signs suggesting developmental delay during early infancy include the quality or inability to support upright standing postion while held by armpits.

Later, inability to walk on heels without compensating at hips suggests upper motor neuron involvement. It is the most common objective sign which can be observed in children with common developmental delay. When in doubt, the child should be asked to take a squatting position. If Achilles tendon is tight, the child is unable to assume a full squatting position. If child continues to do so, he or she is likely to fall backward.

Most children with common developmental delay have normal or increased muscle tone. However, hypotonic type of common developmental delay is not uncommon. A generalized hypotonia in the context of normal or decreased deep tendon reflexes, congenital myopathies or congenital myasthenia should be considered.

A full ophthalmic examination for the status of the optic nerve and retina should be sought actively. Their abnormality will direct the investigation to white matter or grey matter disorders, respectively. The presence of corneal opacity in the context of coarsening of facial features directs investigation towards mucopolysaccharidosis.

Laboratory Investigation

Laboratory investigation and its extent for an etiologic diagnosis is personal to physicians. An etiologic diagnosis in common developmental delay is unlikely because the proposed common neurological profile makes the subject of common developmental delay homogenous by excluding the clinical markers suggestive of a specific etiologic diagnosis.

Almost all children with common developmental disorder with a common neurological profile do not require laboratory testing. Asymptomatic biochemical defects such as thyroid function test, if not done already, is performed universally.

A retrospective study selected nine clinical markers to improve the diagnostic yield of children with global developmental delay. These included sex, severity of global developmental delay, parental consanguinity, family history, behavioral problems, head size, facial dysmorphism, non-facial anomalies, and neurological deficits. Amongst 577 children, mild, moderate, and severe global developmental delay occurred 63%, 33%, and 4%, respectively. An identifiable etiology was found in 53% with genetic disease being the most common (25%). For further diagnostic testing based on statistical analysis, they identified four clinical markers: (1) Severity of global developmental delay, (2) Behavioral problems, (3) Facial dysmorphism, and (4) Neurological deficits [36].

Who needs laboratory investigation? Any child who does not conform to the proposed common neurological profile should be a red flag for further investigation. The caution, a history where the child has lost previously acquired limited vocabulary or emergence of a new movement is not uncommon. These apparent regression do not qualify for a true regression and thus, no laboratory investigation is indicated.

Only few children with such a common neurological profile will need laboratory investigation. The indication for laboratory investigation include: (1) When the child's developmental course is uncertain, (2) Child has cerebral palsy-like syndrome, and (3) When the clinical evaluation indicates a medical or neurological

condition. For example, in the presence of hyporeflexia at ankles suggesting white matter brain disease, skin marks suggesting neurocutaneous disorders, dysmorphism suggesting medical or neuro-genetical disorder, coarsening of facial features suggesting mucopolysaccharidosis, involvement of optic nerve or retina suggesting leukodystrophy or grey matter disorders, respectively. In addition, the presence of specific neurological signs such as supranuclear gaze palsy suggestive of a specific neurodevelopmental disorders should prompt an magnetic resonance (MRI) of the brain [37].

In authors' view, a universal routine testing or MRI of the brain in lack of clinical suspicion of a disease is unlikely to reveal a specific neurological diagnosis. The temptation to take such an approach should be avoided.

Neuroimaging

MRI of the brain is almost always preferred and most commonly performed procedure in the evaluation of children with developmental delay. The results in children with common developmental delay is either normal or reveals incidental finding.

The three most common findings are periventricular leukomalacia, arachnoid cyst, or Chiari malformation type I [38], which are unlikely findings in the context of a developmental regression. The presence of such findings in children with common developmental delay should assure the clinician that (1) The child does not have a neurodegenerative disorder, (2) His or her physical and mental abilities are likely to improve, and (3) This should obviate the need for further investigation.

Brain MRI is recommended in the presence of early preference in the use of limbs suggesting remote intrauterine stroke, dysmorphism, and abnormal head size or shape [39]. In the presence of early preference, MRI is likely to reveal asymmetrical periventricular leukomalacia, remote intrauterine stroke commonly in the distribution of middle cerebral artery or no cerebral abnormalities.

Electroencephalography

Presently, electroencephalography (EEG) is not recommended in evaluating the developmental status of a child. However, during awake a slower than normal background EEG activity for the age could be a useful marker to define developmental delay status.

A case control study investigated EEG activity and its developmental course in ADHD and patients with typical developmental status. The study reported no difference in EEG activity between two groups. The study concluded "A maturational deviation rather than a maturational delay may underlie a subgroup of ADHD. The author of the study questioned the clinical utility of conventional EEG for diagnosis of ADHD [40]. The developmental status of children in the study was unstated.

The majority of children with ADHD do have developmental delay was reported by another study [41]. In this study, developmental delay was defined as delayed milestones according to the Denver II, which is a screening tool.

Nonetheless, a video-EEG is particularly useful in documenting the lack of ictal EEG abnormality in case of children with developmental delay who develop unexplained abnormal movements.

Specialized tests

The following tests should be performed selectively in very limited number of cases.

Inborn errors of metabolism: The purpose is to identify the earliest possible treatable cause of an inborn error of metabolism [42]. This includes serum lactate, pyruvate, ammonia, creatine kinase, quantitative serum aminoacids and urinary organic acids, or urinary mucopolysaccharides. This test should be reperformed in the absence of a universal screening result or in the presence of clinical suspicion.

Chromosomal microarray DNA test: Amongst genetic tests, chromosomal microarray has become a first-line test for evaluation of children with global developmental delay. The G-banded karyotype is frequently utilized as an adjunct to the microarray. Most recently, the clinical availability of whole-genome and whole-exome sequencing has opened new possibilities for the evaluation of children with global developmental delay [43].

A retrospective study of microarray analysis in 82 children was carried-out in children with epilepsy, speech delay, motor impairment, or autism. The clinical variable included mental retardation / delay 73 (89%), autism 16 (19.5%), learning disability 14 (17%), motor impairment 59 (72%), hypotonia 35 (42.7%), dysmorphic features 20 (24.4%), and epilepsy 22 (26.8%). All patients exhibited a normal karyotype. Microarray analysis was abnormal in 20 (23.5%). Deletions comprised 74% of all abnormalities. Patients with ≥ 4 clinical variables demonstrated a 30.5% incidence of abnormal chromosomal microarray findings, compared to 8.7% of patients with ≤ 3 clinical variables ($P = 0.039$, χ^2 test) [44].

It should be noted that chromosomal microarray may be abnormal in children with normal karyotype and unlike common developmental delay, the subjects in this study included autism, mental retardation, and dysmorphic feature. The presence of dysmorphic features, congenital abnormality, features suggestive of a specific hereditary disease, or gender in specific disorders increase yields for microarray abnormality [45].

Nonetheless, in some children with common developmental delay, microarray analysis may reveal abnormality of unknown significance. In the future, chromosomal microarray is likely to replace karyotyping and thus, be used routinely. Contrary to the perception that this approach is more expensive, microarray would be cost-effective as a first genetic test in the clinical evaluation of children with global developmental delay [46].

Fragile X DNA testing is recommended in the initial evaluation, however it is normal in children with common developmental delay.

Any genetic testing beyond microarray analysis should be done in consultation with a medical geneticist, unless physician has suspected or identified clinically a specific condition.

Other specific tests

Laboratory testing for a specific neurological disorder affecting development, such as Rett syndrome, leukodystrophies, mucopolysaccharidoses, or other disorders should be performed in the clinical context suggestive of the individual disorder. The diagnostic work up for hereditary neurodegenerative disorders is complex. The pattern and extent of white matter on MRI of the brain may suggest a clinical diagnosis and guide a specific test in confirmation of the diagnosis.

Diagnosis

Developmental delays with presumed etiology

Common developmental delay should be differentiated from impairments caused by acquired conditions, which include being premature (gestational age less than 37 weeks), adverse perinatal events such as hypoxic ischemic event, congenital infection, fetal alcohol syndrome, and cerebral malformations. Developmental delay caused by these etiologies has a non-regressive course and children's developmental milestones is likely to improve overtime.

Cerebral palsy-like syndrome

Cerebral palsy-like syndromes are rare and should be considered actively if cortical motor involvement occurs in the absence of cognitive delay.

In the presence of dystonic cerebral palsy, look for dopa-responsive childhood-onset dystonia [47]. In the presence of paraplegia, evaluate for arginase deficiency. In the presence of hemiparesis with or without migraine, evaluate for MELAS, and in the presence of quadriplegia, mucopolipidosis type IV or Niemann-Pick disease type C should be considered. Niemann-Pick disease type C should be suspected in the presence of difficulty when going to down the stairs, suggesting supranuclear vertical gaze palsy [48]. Mucopolipidosis type IV is suspected in the presence of diminishing vision secondary to corneal opacity or non-correctible iron deficiency anemia despite an appropriate therapeutic dose and duration of iron administration [49].

Conditions with loss of acquired developmental milestones

Specific syndromes, such as Rett syndrome or Menkes disease, are diagnosed based on their specific neurological features in the background of developmental regression. It should be noted that the majority of disorders affecting regression are the result of neurometabolic disorders of enzyme defect. Thus, these children are born normal at full-term and have no obvious dysmorphisms. The age at which the disease manifests depends upon the residual enzyme activity, lesser is the active enzyme, younger is the onset and severity of the disease.

The clinical diagnosis of children with a common developmental delay should be based on described common neurological profile (Table 3).

A study analyzed the clinical characteristics of children with primary delayed language development ($n = 183$) and a language

delay as a part of a global developmental delay (n = 467). They reported no perinatal risk factor difference in these two groups. Children with global developmental delay had much more delayed acquisition of independent walking and more frequent EEG abnormalities. The positive family history of delayed language development was prevalent in children with primary delayed language development ($p < 0.01$). They concluded that the linguistic profiles of children with language delay could not differentiate between primary and global delayed language developments [50].

Common Comorbidity

Common developmental delay is not a temporary diagnosis. This diagnosis has future consequences of poor qualitative physical and educational performances. The exact prevalence and the type of comorbidities are unknown. In general, developmental delay irrespective of the etiology is associated with a lifelong co-morbidities, which include a learning disability, behavioral problem, or seizure disorder.

Common Management Strategy

The goal of therapy is to optimize physical and mental activity. The common neurological therapies are: (1) Reassurance, (2) Early intervention, and (3) Managing the concurrent or future risks for behavioral problem, learning disability, and epilepsy.

An early clinical diagnosis is desirable to institute an early intervention [51].

Clinical evidence suggests that an early intervention during early infancy has a positive effect on cognitive and speech development, social skills, behavior, and school performance [52, 53].

A long term oral drug therapy with gamma-aminobutyric acid (Baclofen) or periodic injections of onabotulinumtoxin A (Botox) for children with spasticity may be needed [54-56].

Neurological Outcome

Preschool children diagnosed with global developmental delay and language impairment were reassessed by Battelle Developmental Inventory and functional outcome was measured by Vineland Adaptive Behavior Scale. The proportion of children falling below meaningful cut-offs was significantly higher in global developmental delay. The developmental and functional deficits persisted in both subgroups of children [57].

At the first encounter of clinical diagnosis, risk for comorbidities that present later in life should be discussed. The parents should be reassured of medical health wellness of their child.

Litigation

Delay in diagnosis or missing a specific neurodevelopmental disorder can be avoided by adherence to the common neurological profile and by identifying a specific feature suggestive of a particular disease in children with developmental delay.

Future

The developmental delay related studies should define developmental status of their subjects carefully. Future studies statistically analyse the proposed neurological profile in making the clinical diagnosis of children with common developmental delay.

Summary

Most children with common developmental delay are “unnoticed” in general population. They have variable presentations. Rapidly expanding knowledge in the setting of a busy neurological practice demands a clear clinical understanding of the presented developmental problems and its course.

The children with common developmental delay described above are a relatively homogenous population of full-term children with developmental delay of unknown etiology without regression. A lack of specific neurological symptomatology differentiates them from other developmental delay groups.

Based on the past studies, this is the very first report of a common neurological profile in full-term children with common developmental delay. The use of the term “common developmental delay” differentiates the diagnosis from the domains of disability and comorbidity of children with developmental delay. The proposed common neurological profile will empower clinicians in making a clinical diagnosis for common developmental delay.

Once recognized, no laboratory investigations are needed. At times, normal results incite further anxiety and thus, more testing. As a result, a legal implication of delay in diagnosis and management can be avoided. Management strategies includes parental reassurance, early intervention, and future management of comorbidities, namely epilepsy, behavioral problem, and a learning disability.

Acknowledgement

The authors thank to Jason Green, DO for his critical review of this manuscript draft.

Reference

- 1 Kim MS, Kim JK (2010) Assessment of children with developmental delay: Korean-ages & stages questionnaires (KASQ) and Bayley Scales of Infant Development test II (BSID-II). *J Korean Child Neurol Soc* 18: 49-57.
- 2 Shevell MI (2010) Present conceptualization of early childhood neurodevelopmental disabilities. *J Child Neurol* 25: 120-126.
- 3 Hwang AW, Chou YT, Hsieh CL, Hsieh WS, Liao HF, et al. (2015) Developmental screening tool for toddlers with multiple domains based on Rasch analysis. *J Formos Med Assoc* 114: 23-34.
- 4 Aggarwal A, Mittal H, Patil R, Debnath S, Rai A (2013) Clinical profile of children with developmental delay and microcephaly. *J Neurosci Rural Pract* 4: 288-291.
- 5 Pieters S, Desoete A, Van Waelvelde H, Vanderswalmen R, Roeyers H (2012) Mathematical problems in children with developmental coordination disorder. *Res Dev Disabil* 33: 1128-1135.
- 6 Kort W, Compaan EL, Bleichrodt N, Resing WCM, Schittekatte M, et al. (2002). *Wechsler Intelligence Scale for Children (3rd edn.)* London: The Psychological Corporation Limited.
- 7 Wechsler D (1991) *The Wechsler Intelligence Scale for children (3rd edn.)* San Antonio, Texas: The Psychological Corporation.
- 8 Silva LM, Schalock M (2012) Sense and self-regulation checklist, a measure of comorbid autism symptoms: initial psychometric evidence. *Am J Occup Ther* 66: 177-186.
- 9 Schieve LA, Gonzalez V, Boulet SL, Visser SN, Rice CE, et al. (2012) Concurrent medical conditions and health care use and needs among children with learning and behavioral developmental disabilities, National Health Interview Survey, 2006-2010. *Res Dev Disabil* 33: 467-476.
- 10 Baker BL, Neece CL, Fenning RM, Crnic KA, Blacher J (2010) Mental disorders in five-year-old children with or without developmental delay: focus on ADHD. *J Clin Child Adolesc Psychol* 39: 492-495.
- 11 Bayley N (1993) *Bayley Scales of Infant Development: Manual (2nd edn.)* San Antonio, Texas: Psychological Corporation.
- 12 Tang KM, Chen TY, Lau VW, Wu MM (2008) Clinical profile of young children with mental retardation and developmental delay in Hong Kong. *Hong Kong Med J* 14: 97-102.
- 13 De S, Small J, Baur LA (2008) Overweight and obesity among children with developmental disabilities. *J Intellect Dev Disabil* 33: 43-47.
- 14 Griffiths R (1984) *The abilities of young children.* Hong Kong: The Test Agency Limited.
- 15 Bernabei P, Fenton G, Fabrizi A, Camaioni L, Perucchini P (2003) Profiles of sensorimotor development in children with autism and with developmental delay. *Percept Mot Skills* 96: 1107-1116.
- 16 Keating D, Turrell G, Ozanne A (2001) Childhood speech disorders: reported prevalence, comorbidity and socioeconomic profile. *J Paediatr Child Health* 37: 431-436.
- 17 Eom S, Fisher B, Dezort C, Berg AT (2014) Routine developmental, autism, behavioral, and psychological screening in epilepsy care settings. *Dev Med Child Neurol* 56: 1100-1105.
- 18 Gergev G, Máté A, Zimmermann A, Ráosi F, Sztriha L (2015) Spectrum of neurodevelopmental disabilities: a cohort study in Hungary. *J Child Neurol* 30: 344-356.
- 19 Fenichel GM (2013) *Clinical Pediatric Neurology.* Philadelphia, WB Saunders.
- 20 Petersen MC, Kube DA, Palmer FB (1998) Classification of developmental delays. *Semin Pediatr Neurol* 5: 2-14.
- 21 Curry CJ, Stevenson RE, Aughton D, Byrne J, Carey JC, et al. (1997) Evaluation of mental retardation: recommendations of a Consensus Conference: American College of Medical Genetics. *Am J Med Genet* 72: 468-477.
- 22 Bertrand J (2016) Fetal alcohol spectrum disorders are clearly brain-based. *Dev Med Child Neurol.*
- 23 Gupta SN, Gupta VS, Borad N (2015) CNS complication of Group A streptococcal meningitis in children: A comprehensive case-based literature review. *Neuro Open J* 2: 31-37.
- 24 Gupta SN, Gupta VS, Borad N (2015) Late Onset Neonatal Herpes Encephalitis: A Case-Based CNS Complication and Neurological Outcome. *Open Access Library Journal* 2: 1280.
- 25 Mian M, Shah J, Dalpiaz A, Schwamb R, Miao Y, et al. (2015) Shaken Baby Syndrome: a review. *Fetal Pediatr Pathol* 34: 169-175.
- 26 Ozawa T, Koide R, Nakata Y, Saitsu H, Matsumoto N, et al. (2014) A novel WDR45 mutation in a patient with static encephalopathy of childhood with neurodegeneration in adulthood (SENDA). *Am J Med Genet A* 164: 2388-90.
- 27 Kanner L (1943) Autistic Disturbances of Affective Contact. *Nervous Child* 3: 217-250.
- 28 Rutter M, Bartak L (1971) Causes of Infantile Autism: Some Considerations from Recent Research. *J Autism Child Schizophr* 1: 20-32.
- 29 Kim SK (2015) Recent update of autism spectrum disorders. *Korean J Pediatr* 58: 8-14.
- 30 Boudry-Labis E, Demeer B, Le Caignec C, Isidor B, Mathieu-Dramard M, et al. (2013) A novel microdeletion syndrome at 9q21.13 characterised by mental retardation, speech delay, epilepsy and characteristic facial features. *Eur J Med Genet* 56: 163-170.
- 31 Bax M (1964) Terminology and classification of cerebral palsy. *Dev Med Child Neurol* 6: 295-307.
- 32 Soucy EA, Gao F, Gutmann DH, Dunn CM (2012) Developmental delays in children with neurofibromatosis type 1. *J Child Neurol* 27: 641-644.
- 33 Lobo MA, Paul DA, Mackley A, Maher J, Galloway JC (2014) Instability of delay classification and determination of early intervention eligibility in the first two years of life. *Res Dev Disabil* 35: 117-126.
- 34 Strand KE, Augustyn M (2015) Apraxia, autism, attention-deficit hyperactivity disorder: do we have a new spectrum? *J Dev Behav Pediatr* 36: 124-126.
- 35 Matsuoka M, Nagamitsu S, Iwasaki M, Iemura A, Yamashita Y, et al. (2014) High incidence of sleep problems in children with developmental disorders: results of a questionnaire survey in a Japanese elementary school. *Brain Dev* 36: 35-44.
- 36 Wong VC, Chung B (2011) Value of clinical assessment in the diagnostic evaluation of Global Developmental Delay using a Likelihood Ratio Model. *Brain Dev* 33: 548-557.
- 37 Vedolin L (2011) Inherited white matter disorders of childhood: a magnetic resonance imaging-based pattern recognition approach. *Top Magn Reson Imaging* 22: 215-222.

- 38 Gupta SN, Kanamalla U, Gupta V (2010) Are incidental findings on brain magnetic resonance images in children merely incidental? *J Child Neurol* 25: 1511-1516.
- 39 Shevell M, Ashwal S, Donley D, Flint J, Gingold M, et al. (2003) Quality Standards Subcommittee of the American Academy of Neurology; Practice Committee of the Child Neurology Society. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. *Neurology* 60: 367-380.
- 40 Buyck I, Wiersema JR (2014) Resting electroencephalogram in attention deficit hyperactivity disorder: developmental course and diagnostic value. *Psychiatry Res* 216: 391-397.
- 41 Gupta SN, Gupta VS (2014) Prevalence of Developmental Delay in Children with Attention-Deficit/Hyperactivity Disorder: Neurologic Perspective. *Austin J Neurol Disord Epilepsy* 1: 4.
- 42 Stockler-Ipsiroglu S, van Karnebeek CD (2014) Cerebral creatine deficiencies: a group of treatable intellectual developmental disorders. *Semin Neurol* 34: 350-6.
- 43 Flore LA, Milunsky JM (2012) Updates in the genetic evaluation of the child with global developmental delay or intellectual disability. *Semin Pediatr Neurol* 19: 173-180.
- 44 Ezugha H, Anderson CE, Marks HG, Khurana D, Legido A, et al. (2010) Microarray analysis in children with developmental disorder or epilepsy. *Pediatr Neurol* 43: 391-394.
- 45 Henderson LB, Applegate CD, Wohler E, Sheridan MB, Hoover-Fong J, et al. (2014) The impact of chromosomal microarray on clinical management: a retrospective analysis. *Genet Med* 16: 657-664.
- 46 Trakadis Y, Shevell M (2011) Microarray as a first genetic test in global developmental delay: a cost-effectiveness analysis. *Dev Med Child Neurol* 53: 994-999.
- 47 Lee JH, Ki CS, Kim DS, Cho JW, Park KP, et al. (2011) Dopa-responsive dystonia with a novel initiation codon mutation in the GCH1 gene misdiagnosed as cerebral palsy. *J Korean Med Sci* 26: 1244-1246.
- 48 Stampfer M, Theiss S, Amraoui Y, Jiang X, Keller S, et al. (2013) Niemann-Pick disease type C clinical database: cognitive and coordination deficits are early disease indicators. *Orphanet J Rare Dis* 8: 35.
- 49 Altarescu G, Sun M, Moore DF, Smith JA, Wiggs EA, et al. (2002) The neurogenetics of mucopolidosis type IV. *Neurology* 59: 306-313.
- 50 Kim SW, Jeon HR, Park EJ, Chung HJ, Song JE (2014) The differences in clinical aspect between specific language impairment and global developmental delay. *Ann Rehabil Med* 38: 752-758.
- 51 Jimenez-Gomez A, Standridge SM (2014) A refined approach to evaluating global developmental delay for the international medical community. *Pediatr Neurol* 51: 198-206.
- 52 Nair MK, Mini AO, Leena ML, George B, Harikumar Nair GS, et al. (2014) CDC Kerala 7: Effect of Early Language Intervention Among Children 0-3 y with Speech and Language Delay. *Indian J Pediatr* 81: 102-109.
- 53 Lawrence R, Bateman N (2013) 12 minute consultation: An evidence-based approach to the management of a child with speech and language delay. *Clin Otolaryngol* 38: 148-153.
- 54 Schramm A, Ndayisaba JP, Auf dem Brinke M, Hecht M, Herrmann C, et al. (2014) Spasticity treatment with onabotulinumtoxin A: data from a prospective German real-life patient registry. *J Neural Transm* 121: 521-530.
- 55 Hoare B (2015) Constraint therapy, the panacea for unilateral cerebral palsy? *Dev Med Child Neurol* 57: 12-13.
- 56 Schrank J (2013) Constraint-induced movement therapy effects on gross motor function of a child with triplegic cerebral palsy. *Pediatr Phys Ther* 25: 71-78.
- 57 Shevell M, Majnemer A, Platt RW, Webster R, Birnbaum R (2005) Developmental and functional outcomes in children with global developmental delay or developmental language impairment. *Dev Med Child Neurol* 47: 678-683.