

Genetics and the investigation of developmental delay/intellectual disability

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ABSTRACT

Global developmental delay and intellectual disabilities are common reasons for diagnostic assessment by paediatricians. There are a multiplicity of possible causes many of which have genetic, management and treatment implications for the child and family. Genetic causes are estimated to be responsible for approximately a quarter to one-half of identified cases. The multiplicity of individually rare genetic causes challenges the practitioner with respect to the selection of diagnostic tests and accurate diagnosis. To assist the practitioner practice guidelines have been formulated and these are reviewed and summarised in this particular article.

CLINICAL FEATURES

Understanding the clinical features of global developmental delay and intellectual disability is an essential precondition to accurate and reliable diagnosis. These are complementary chronologically framed entities that encapsulate heterogeneous 'symptom complexes' frequently encountered in paediatrics.¹ Global developmental delay is defined as a significant functional delay in two or more developmental domains (eg, motor (gross/fine), speech/language (expressive, receptive, mixed), cognition, personal-social and activities of daily living).² Intellectual disability has supplanted the term 'mental retardation' which should be avoided as pejorative terminology. The 'new' term reflects an alteration in the construct of disability that increasingly emphasises contextual factors and adaptive behaviours, rather than a single objective measurement in contrast to an arbitrary 'normative' construct. Originally formulated in strictly psychometric terms as performance greater than 2.5SDs below the mean on intelligence testing, the conceptualisation of intellectual disability has been extended to include defects in 'adaptive behaviour as expressed in conceptual, social, practical and adaptive skills'.³ Employing assessments that incorporate sensitivity to cultural and linguistic diversity, limitations for the individual with intellectual disability are apparent within varied environments. These limitations are present from an early age, exist across the lifespan and require the implementation of systems of support to maximise individual participation in all environments. The use of the term 'intellectual disability' is largely restricted to individuals older than 5 years of age, while that of global developmental delay is applied to the child aged 5 years or less.³

As 'symptom complexes', global developmental delay and intellectual disability are in essence never the same disorder twice. Presentations, underlying aetiologies, associated comorbidities, medical

challenges, rehabilitation service needs, individual trajectories and eventual outcomes vary.⁴ Their relative merits as meaningful constructs rest on a commonality of approach, evaluation and management principles. Global developmental delay reflects a parental emphasis on a child's attainment of developmental competencies and skills as a prelude to successful individual autonomy. Intellectual disability reflects our distinctive human capacity to reason, think abstractly and plan that are preconditions to our ability to learn, solve problems and truly comprehend our surroundings.⁵ These entities are obviously inter-related in that many individuals originally diagnosed with 'global developmental delay' will later merit a diagnosis of 'intellectual disability'.

Given the normative population-wide distribution of developmental and intellectual skills, global developmental delay and intellectual disability will not unexpectedly affect between 2% and 3% of the population.³ Roughly two-thirds of affected individuals will have a mild-to-moderate level of impairment, while one-third will have a severe-to-profound level of impairment. Men are more affected than women and there appears to be an inverse socioeconomic status gradient with respect to prevalence. The gender and socioeconomic bias noted appear to be operative for mild-to-moderate degrees of impairment only. Individuals with global developmental delay or intellectual disability are at an increased risk for a variety of comorbidities, including epilepsy or convulsive disorders, behavioural disturbances, attentional limitations, psychiatric illness and sensory impairments (ie, vision and hearing). The full economic impact of these disorders remains unknown, although a recent study places additional lifetime costs per individual at close to \$1 million, with a lifetime additional cost for medical care above \$50 billion for the cohort of US children born in the year 2000 with an intellectual disability.⁶

Aside from classifying according to the severity of observed impairment, some authors have distinguished between syndromic and non-syndromic developmental delay or intellectual disability.⁷ Syndromic intellectual disability or developmental delay is said to occur when in addition to observed delay or intellectual disability a distinct clinical phenotype (eg, Trisomy 21) may be apparent or comorbidities in addition to intellectual disability are readily evident. The documentation of dysmorphic features or congenital anomalies in non-CNS organ systems may also suggest a syndromic subclassification. Non-syndromic intellectual disability or delay is defined by intellectual disability being the sole discernable clinical feature.

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AETIOLOGY

Understanding the possible aetiological spectrum for global developmental delay and intellectual disability provides a rationale for relevant testing. The aetiology of global developmental delay and intellectual disability as befitting their characterisation as 'symptom complexes' is quite heterogeneous. Causes may be congenital or acquired with a prenatal, perinatal or postnatal timing of acquisition. Over the past decade, various groups have formulated practice parameters and guidelines to assist the clinician in the standardised evidence-based evaluation of these entities.^{2 8–10} At present, it appears that between a quarter to one-half of identified causes are genetic in origin. Genetic aetiologies are multiple and include chromosomal anomaly (eg, aneuploidies), submicroscopic deletions/duplications/rearrangements (eg, copy number variant changes) and monogenic disorders.¹¹ Indeed to date 450 genes have been implicated in intellectual disability, with 400 attributed to syndromic intellectual disability and 50 to non-syndromic intellectual disability. All manner of Mendelian inheritance (autosomal dominant, autosomal recessive and X linked) have been documented with the bulk of genes known to result in non-syndromic intellectual disability having a X-chromosome location. Although the number of genes known to be implicated in intellectual disability has increased substantially over the last decade, the majority of suspected genetic causes presently lack a specific molecular diagnosis. At present, only a few specific well-characterised single gene associations with a highly recognised clinical phenotype (ie, FMR1-Fragile X and MECP2-Rett syndrome) are routinely tested for at a molecular level during diagnostic evaluation.¹⁰ In addition to the nuclear genome, defects in the mitochondrial genome can give rise to syndromic intellectual disability featuring a maternal pattern of inheritance.

Progress in the identifications of genes responsible for global developmental delay and intellectual disability has furthered our understanding of the molecular basis for learning and memory that is fundamental for comprehending cognition and intellect from a neurological perspective.^{7 11} An increasing knowledge of molecular pathways will enable the eventual rational selection of pharmacologic and candidate gene therapeutic approaches. Furthermore, while there may be evidence for a bewildering array of genes involved, there appears to be a merger of gene action into several discrete networks of functional processes that yield a convergence of phenotypes of intellectual disability. These basic processes include neurogenesis (ie, neuronal proliferation), neuronal migration, interneuronal connectivity (ie, presynaptic vesicle formation, synaptogenesis, synaptic plasticity, dendrite morphogenesis and postsynaptic density), cellular signalling cascades and the broad regulation of transcription and translation (both genetic and epigenetic in origin) functions.

DIAGNOSIS

Accurate diagnosis of global developmental delay or intellectual disability is an essential precondition to initiating a proper evaluation relevant to service referrals, appropriate ongoing management directed at expected comorbidities and counselling that meets the needs of families.^{12 13} This diagnosis is predicated on careful attention to the operational definition of these entities as outlined above. The diagnosis is typically formulated initially on the basis of clinical judgement. The validity of such a diagnosis is related to the degree of direct experience with these individuals by the diagnostician. Validity is increased by clinical observation, multiple inputs from reliable third-party informants (eg, educators), repeated observations over time and

input either concurrently or subsequently from an interdisciplinary professional team offering complementary skill sets (eg, physicians, occupational therapists, physiotherapists, speech language pathologists and psychologists). A contextual sensitivity to social, cultural and linguistic diversity is also especially pertinent. Indeed, such varying contexts may preclude the availability for administration of standardised evaluations that are the hallmark of an objective corroborating diagnosis of developmental delay or intellectual disability.

A diagnosis of global developmental delay is chronologically limited typically to children less than 5 years. Hence for this diagnosis there is a reliance on accepted widely used standardised measures of developmental performance and attainment in the young child that are psychometrically robust. Measures generally acknowledged to meet this threshold include the Bayley Scales of Infant Development, 2nd edition and the Battelle Developmental Inventory. An indirect evaluation measure that uses third-party reports is the Child Development Inventory.¹³

A variety of widely used standardised measures for cognitive function exist.¹⁴ To qualify for a diagnosis of intellectual disability, performance greater than 2.5SDs below the mean is expected. Those administering a test must be trained and experienced in its application, and interpretation requires an awareness of the applied test's standard error of measurement (SEM). Routinely used measures in practice include the Wechsler Intelligence Scales for Children, 4th edition, the Wechsler Preschool and Primary Scales of Intelligence, 3rd edition and the Sanford-Binet Intelligence Scales, 5th edition. To merit the diagnosis of intellectual disability, concurrent deficits in adaptive behaviour must also be demonstrated. Typically these can be obtained in an indirect way through functional ratings obtained through systematic interviews of a parent or caregiver. An example of one such widely used measure of adaptive behaviour is the Vineland Adapted Behaviour Scale, 2nd edition.

An important component of accurate diagnosis for both global developmental delay and intellectual disability includes the delineation of any autistic features meriting the possible diagnosis of an autistic spectrum disorder.¹⁵ If autistic features are suspected on the initial clinical assessment, a trio of standardised autism diagnostic tools is readily available in practice. These include the Autism Diagnosis Observation Scale, the Autism Diagnosis Inventory and the Childhood Autism Rating Scale.¹⁴

EVALUATION AND TESTING

The diagnostic evaluation of global developmental delay and intellectual disability begins with a detailed history^{8 10 12 13} Particular attention needs to be directed to potential clues for a genetic or acquired aetiology. A genetic aetiology may be suspected by family history, parental consanguinity, prior stillbirths or postnatal deaths of prior offspring. Antenatal history may ascertain adverse toxic or infectious exposures or substantive intrauterine difficulties. Labour, delivery and neonatal historical details are of essence in identifying a potentially causal perinatal event. Furthermore, developmental progression, possible regression and current developmental and functional status must be determined. Possible coexisting medical conditions must be elicited as these will impact on future management as well as the presence or absence of appropriate rehabilitation service provision.

The requisite physical examination of the affected child begins with an informed indirect observation throughout history taking. Ideally this should be in a setting that enables the

formulation of an awareness of the child's current developmental, functional and cognitive skills. Specific aspects of the physical examination of interest include measurements of height, weight and head circumference and screening for dysmorphology, hepatosplenomegaly, the cutaneous stigmata of a phakomatosis, spinal dysraphism, as well as the integrity of the hearing and vision apparatus. This needs to be accompanied by a thorough neurological examination that may yield clues to localisation and as full as possible developmental, functional and cognitive assessments as permitted by individual cooperation.

Laboratory testing is directed towards the determination of an underlying aetiological cause for an individual's developmental delay or intellectual disability, with a particular emphasis on possible treatable causes. Recent consensus papers have assisted the clinician by the formulation of an approach based on a systematic review of the relevant literature.⁷⁻⁹ The consensus recommendations incorporate both the use of specific identifying clinical features to suggest disease-specific testing based on a heightened pretest probability and screening investigations with an established greater than 1% yield. Indeed, if subsequent to history and physical examination a specific aetiology is suspected, then testing is singularly directed and focused on confirming this diagnostic suspicion. Algorithms that are applicable to the clinical context are contained in these consensus papers.⁷⁻⁹

In the absence of a strong specific aetiological suspicion subsequent to history and physical examination, present consensus opinion suggests the following diagnostic approach.^{8, 10} Chromosomal Microarray Analysis (CMA) (ie, comparative genomic hybridisation, single nucleotide polymorphism) directed at the determination of potentially pathogenic genomic structural variations in DNA copy number is the single test with the highest aetiological yield in this particular clinical setting. Briefly, the method of CMA consists of differentially labelling patient and reference DNA with two fluorophores, competitively hybridising the labelled DNA to genomic DNA targets and comparing for variations in DNA copy number. CMA essentially functions as a karyotype with a 100-fold higher resolution. It is technically unable to detect balanced translocations. One of the major challenges of CMA is the interpretation of an 'abnormal' result, and the determination of whether or not it is pathogenic. Guidelines for the interpretation of CMAs are available.¹⁶ The first step is testing the parents to determine whether the CNV is de novo, in which case it is more likely pathogenic. Inherited CNVs from a phenotypically normal parent are usually benign. However, many CNVs have been reported to have variable or incomplete penetrance, thus caution must be taken when counselling families. Publicly available only databases such as the Database of Genomic Variants (<http://projects.tcag.ca/variation/>) and the database DECIPHER (<https://decipher.sanger.ac.uk/>) catalogue chromosomal imbalances and list the associated phenotypes with appropriate references. Further genetic testing that can be conducted include a creatine kinase level for muscular dystrophy (as muscle weakness may not be overt early), determining a possible FMR1 triplet expansion that underlies Fragile X syndrome in all individuals and MECP2 analysis for Rett syndrome in moderately-to-severely impaired women. An X linked inheritance pattern evident in a particular family will direct testing preferentially towards a group of now identified X chromosome located genes predominantly involved in synaptic function. Additionally, high-resolution MRI provides the detection of cerebral dysgenesis (some of which have a known genetic relationship) and acquired injuries (cortical and subcortical; grey and/or white matter

involvement). When paired with proton spectroscopy, there exists the potential for detection of central mitochondrial disorders (ie, lactate peaks) and disorders of creatine deficiency.

Consideration must also be given to diagnostic testing targeting inborn errors of metabolism, especially those that are amenable to causally beneficial therapy. At present 81 such disorders have been delineated. A recent review highlights that 65% of such disorders can be identified by first-tier screening tests that are both generally available and inexpensive.¹⁷ Such first-tier testing includes serum ammonia, lactate, copper, ceruloplasmin, homocysteine, plasma amino acids, urine organic acids, purines, pyrimidines, creatine metabolites, oligosaccharides and glycosaminoglycan. Such first-tier testing must be considered when no diagnosis is evident following history or physical exam and completion of microarray, imaging, FMR1 and MECP2 testing. The remaining treatable inborn errors of metabolism can only be diagnosed by second-tier testing that are characterised by a highly specific orientation (eg, CSF neurotransmitter analysis) that features a 'single test for a single disease' yield that is directed primarily by careful phenotypic recognition. Such recognition is typically dependant on the subspecialty input of a medical or biochemical geneticist. To assist in the diagnosis and management of these treatable inborn errors of metabolism, a recent freely available smart phone App (<http://www.treatable-id.org>) has been developed and disseminated for clinical use. This App contains readily available information on metabolic testing and the related disorders diagnosed.

CONCLUSION

Rapid advances in genetic diagnostic technology will in the very near future enable the clinical introduction on a widespread basis of next-generation sequencing, whole genome sequencing and whole exome sequencing.¹⁰ A particular challenge will be the interpretation of results of particular relevance to a single individual and family. Family-based analysis using trios (affected individual and parents) will likely emerge as the methodology of choice to detect de novo point mutations that are linked causally to global developmental delay and intellectual disability. The widespread application of such technology and the demonstration of its utility and cost-benefits in practice still require validation in clinical population samples. On this basis, with the generation of evidence derived from clinical populations, one can confidently expect alterations in our diagnostic approach in the near-to-intermediate term.

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