Investigating a Child With Developmental Delay

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- Concern about child development a common reason for referral to a Paediatrician

- Developmental Disability +- 10% of children worldwide.

- Non specific presenting complaint for a range of disorders.

- Low frequency high morbidity conditions usually present early eg. Cerebral Palsy, Severe sensory impairments, severe intellectual disability

- High frequency, lower morbidity conditions often present later eg. Academic learning disability, ADHD
Development is a continuous and sequential process which can be interrupted at any given time temporarily or permanently.

Delay in acquisition of skills that are directly observable and measurable in the context of natural progression of all children. Simeonsson & Simeonsson 2001

Chronic Illness is a common cause of neuro-developmental disability esp. in vulnerable communities.

Investing in Early Childhood development is the most cost effect period in which to intervene in the overall management of disability. www.thelancet.com(369)2007
The dilemma

- Many presentations, aetiologies and independent variables.
- There is no strict line between normal and abnormal.
- In South Africa clinicians are often faced with children exposed to multiple risk factors ie. Biological, environmental, social, genetic.
- Multiple risk factors can amplify each other.
Consensus

- There is no single approach to a diagnostic process.

- Investigations must be guided by a detailed history and detailed clinical examination.

- The general paediatricians location determines timing & availability of referrals to Neurology/Dev Paed/Geneticist, Audiology, Ophthalmology, access to newborn metabolic screening.

- The approach to diagnosis must be optimal for a particular child & family.
In reality

- Unless the history and clinical examination provide insight into the diagnosis, early referral or consultation is advisable before embarking on costly undirected investigations.
The Spectrum of Disorders

Global Developmental Delay: GDD
Significant delay in 2/> developmental domains ie. Gross/fine motor, speech/lang, cognition, social/personal, activities of daily living. Often refers to the younger child < 5years. (prevalence ??1-3%)

Main diagnostic categories:
1. Cerebral Dysgenesis eg. Lissencephaly, Schizencephaly, Neuronal migration .
2. Intrapartum Asphyxia
3. Antenatal toxin exposure eg. FAS
4. Genetic Syndromes
5. Chronic Illness eg. HIV
6. Profound psychosocial neglect.
Intellectual Disability/ Mental Retardation

- refers to older children found to have impaired intelligence on valid, reliable IQ testing
- *Must be 2 standard deviations or more less than the mean.*
- *Not all children with GDD have Intellectual Disability eg. Cerebral Palsy, Neuromuscular conditions, severe environmental deprivation*
The Spectrum cont.

- **Developmental Language Impairment**: receptive&/expressive language deficits in the absence of cognitive delay, hearing loss or autistic features.

- **Autistic Spectrum Disorders**: the triad of speech&language delay, impaired social skills & restrictive repetitive patterns of behaviour.

- **Cerebral Palsy**

- **Specific/ Focal Deficits** eg. Hearing, Vision, Specific Learning Disability

- **Syndromes** with specific Developmental Phenotypes eg. Downs, FAS, Williams, Prader Willi
Identification of an aetiology Shevell et al.

Pediatrics 118(1) 2006
- Unselected group of children with Global Dev Delay: n=261
- Mean age 33.6 months
- Aetiology found in 40%
- 55% in the absence of coexisting Autistic features.
- Varies between 40-70%
Overall- rule of 1/3rds in GDD


- Of the 54% of cases where a cause was found:
  - a third were on history and examination alone.
  - a third are diagnosed by confirming clinical suspicion with specific directed investigations.
  - a third on investigations alone, where history & examination are inconclusive.

> 50% of cases are preventable
Diagnostic Categories

- where a cause is likely to be found (> 50% of cases)
  - Global Developmental Delay
  - Isolated Motor Delays
  - Cerebral Palsy

- a cause is unlikely to be found (<5%)
  - Developmental Language Disorders
  - Autism Spectrum Disorders
Finding a Cause helps with:

- Prognosis
- Recurrence risk
- Possible therapeutic options
- Complications
- Acceptance
- Medico-Legal
The Guided Approach to Investigation

- Identify the child at risk early.
  - single or multiple: Preterm
  - SGA
  - LBW
  - neonatal encephalopathy
  - Congenital Heart Disease
  - Low SES
  - FTT
  - Chronic Medical condition eg. HIV
  - family disruption

- Regular Surveillance
- Developmental Evaluation
Clues from the history

- History and physical examination may be sufficient to suggest underlying aetiology.
- Investigations for confirmation.

- Some imp predictors: - abnormal prenatal/ perinatal hx
  - female sex
  - the absence of autistic features
  - microcephaly
  - dysmorphology
  - abnormal neurology esp. focal/ lateralising signs

*The severity of the observed delay is not a predictor of success in determining an underlying cause.

Shevell et al, Pediatrics 118(1) 2006
The History

- Adverse prenatal, peri-natal or post natal events
- Pregnancy losses, early neonatal or infantile deaths
- Consanguinity
- 3 generation family pedigree
- Maternal prescription drugs, alcohol, illicit drug use

??Precise ethnicity, geographic origin.

Discriminating Features
- Short palpebral fissures
- Flat midface
- Short nose
- Indistinct philtrum
- Thin upper lip

Associated Features
- Epicanthal folds
- Low nasal bridge
- Minor ear anomalies
- Micrognathia
On examination- Red Flags

- Motor Impairment/ localising signs
- Microcephaly/Macrocephaly
- Syndromic/ Dysmorphic appearance
- Subtle dysmorphology/ ‘different appearance’
- Neurocutaneous manifestations
- Cardiac anomaly and developmental delay
- Coarse facial features
- HSM
- Eyes: Cataracts, visual impairment
Prioritise investigations

- Optimal Developmental Potential
- Cost Consciousness

- Static Insult
- Progression
- Regression
- Exacerbating factors
- Multiple risk factors

Eg. A child with cerebral palsy and a seizure disorder warrants seizure control + EEG first prior to neuro-imaging. *Uncontrolled epilepsy worsens the developmental outcome!
Modalities available

- Detailed History and examination
- Neuro-imaging: CT Scan
  - MRI
- Genetic Evaluation: Clinical
  - Cytogenetic testing
  - Molecular Genetics
- Metabolic Screening
- EEG
- Vision and Hearing
Neuro-imaging

- Probably most widely available.
- Most useful in the context of global developmental delay with motor impairment ie. CP, Cerebral Dysgenesis.
- Microcephaly & lateralising signs increase yield.
- If available MRI is preferential.
- CT Scan indications: suspected perinatal infection: calcification abnormality of skull bones.

- Is probably justifiable as the 1st Investigation in GDD in the absence of Dysmorphism &/ a family history & with motor delay.
- The finding of a brain anomaly may not be the final diagnosis.

American Academy of Neurology: Practice
Parameter: Evaluation of the child with GDD.
Neuroimaging: Yield of >60% Arch.Dis.Child 2006:91

- Abnormal head size
- Seizures
- Neurological Signs: cranial nerve abnormalities
  - Cerebral palsy
- Dysmorphic facies
- Arthrogryposis
- Severe visual Impairment
  - Optic Atrophy
  - Nystagmus
Example

- Case KK: male
  
  Normal birth history.
  Uncomplicated VSD diagnosed antenatally
  at 6 months: concern about developmental delay
  Normal head circumference
  non specific subtle dysmorphic features
  head lag and decreased truncal tone
  hypertonic with brisk DTR’s
  No history of seizures

  Global developmental delay: ? Cause

  CT brain: global atrophy
  Chromosomes: 46XY

- MRI brain: **Neuronal Migrational abnormality: Lissencephaly with Pachygyria/agyria**
A, Type I lissencephaly, agyria type. Axial T2-weighted image shows a brain with a "figure-8" configuration secondary to the immature Sylvian fissures. A band of neurons (arrows) that was arrested during migration lies between the thin cortex and the lateral ventricles.

B, Type I lissencephaly, pachygyria type.

C, Type I lissencephaly, pachygyria type. Axial T2-weighted image shows broad, flat gyri with shallow sulci throughout the cerebrum.
Genetic Evaluation

- Evidence supports detailed dysmorphology examination and syndrome recognition by experienced clinical geneticists.

- Reality......not always feasible.

- Chromosomal analysis yields the highest no. of abnormalities in GDD even in the absence of clinical clues. Mc Donald L et al; Arch. Dis. Child 2006;91:701-5

- **Laboratory Investigations: Cytogenetics/ Karyotyping**-
  - in unexplained global developmental with or without autistic features +- 3.7%
  
  - The presence of 2/> dysmorphic features increases this yield to 20%

  Shevell et al; Neurology;2009
Indications for Karyotyping

- Dysmorphic features / Syndromic appearance
  Either to confirm a suspected syndrome, most commonly Downs.

- Unexplained Global Developmental delay.
- Unexplained Intellectual Disability
- Family History on 3 generation family pedigree of developmental delay, ID, psychiatric diagnoses.
Syndromes with recognisable phenotypes

Individually Rare

Review of history, clinical features followed by a literature review, OMIM, Smiths

Syndromes which may prompt specific testing:

- Prader Willi
- Angelman
- Rett Syndrome
- Cardiofacial Syndromes: Williams,
  22Q deletion
Prader Willi Syndrome

In Utero: ↓ fetal movt.
At birth: hypotonia
Infancy: FTT
Childhood: Hyperphagia, Speech delay
Adolescence: Obesity
    Short Stature
Paternal 15Q deletion
Angelman Syndrome

• Normal at birth
• Feeding problems
• Developmental delay noted by 6 – 12 months
• Seizures by 2-3 years
• Microcephaly and intellectual disability
• Movement and balance problems/ ataxia
• Happy, excitable demeanor ....’happy puppet’
• Sleep disturbance
• Maternal 15Q deletion
Rett Syndrome

- An impt cause of severe ID in females
- Mutations in the Xlinked MECP2 gene
- Overall prevalence is rare: 1-3/10000
- May be normal in appearance until +- 6months
- Gradual regression of speech and purposeful hand movements
- Abnormal deceleration of head growth:-microcephaly
- Seizures, autistic-like behaviour, ataxia, intermittent hyperventilation and stereotypic hand movements.
- Early demise
Fragile X Syndrome

- The most commonly inherited disorder causing Intellectual disability in males and a significant cause in females.
- Due to a mutation of the FMR gene on the X Chromosome.

- Molecular genetic testing for Fragile X determines 4 forms of the CGG trinucleotide repeat mutations:
  - normal (6-40)
  - intermediate (41-60)
  - premutation (61-200)
  - full mutation (>200)

- Prevalence of the full mutation associated with Dev Delay ranges from 1 in 3717 to 8918 males.
- 1 in 246 to 468 females are carriers.
- +- 1/3 of affected females with a full mutation have mild to severe ID
Fragile X

- **Clinical Phenotype**
  long narrow face, large ears, arched palate, hyperextensible joints, all become more obvious with age, & develop large testes

- **Developmental Phenotype**
  Typically delay in Language & Social domains, with autistic behaviours, attentional difficulties, mood instability, progress to psychiatric features in adolescence & adulthood.
Diagnostic yield

- Family history on 3 generation family pedigree & clinical pre selection increases diagnostic yield.

- Mixed population (males and females) average yield of 2.6%, increases to 5.3% in males only.

- Important to test all siblings (female carriers)

Genetic Implications
On the horizon-Molecular Genetics
In consultation!

- High resolution karyotyping (>550 bands)- aims at finding smaller chromosomal rearrangements.
- Submicroscopic Subtelomeric Rearrangements- often undetected by normal karyotyping.
- MLPA’s (Multiplex Ligation dependant probe amplification)
  Submicroscopic Subtelomeric Rearrangements
- Copy Number Variants_ to detect abnormal copy numbers of DNA sequences across the genome.
Metabolic Screening

- In the context of unexplained Global developmental delay.
- Routine Screening: Low yield of 1%
- Neonatal screening programmes: TFTS, amino and organic acids, mass spectrometry, has increased the diagnosis of metabolic disorders.
- Fear of missing a treatable condition!
- Most children with an IEM have other symptoms: FTT, dev regression, episodic decompensation or physical findings eg. Coarse facial features, HSM, neurologic abnormalities, ophthalmology
- Non specific and non diagnostic abnormalities are frequent, increasing cost and anxiety.
Metabolic tests

- Unexplained GDD: check TFT’s
- Further testing if: consanguinity, family hx, dev regression, episodic decompenation, or physical findings increases yield to 5%

- TFTs, Capillary blood gas, Serum lactate & ammonia, serum amino, and urine organic acids.

- When stepwise screening is performed (consultation) the yield may increase to 14%
EEG

- Evidence supports EEG in the presence of a history or examination features suggesting Epilepsy or seizures, in the context of GDD.

- Have a high index of suspicion in structural anomalies of the brain, history of asphyxia, CP or other cerebral insults.
- Be aware of atypical seizure presentations.
- NB* Infantile
- Undiagnosed persistent seizures worsens the neurological outcome.
Vision and Hearing

- Seen in the context of Universal Newborn screening of vision (clinical, red reflex, surveillance) and hearing (OAE’s, behavioural audiometry)

- Children with Global dev delay are at much higher risk of sensory impairments.
- Impact on management and rehab
- Are often correctable, and may improve outcome.
Summary: Evaluation of GDD

1. Detailed hx & examination
2. Auditory & Ophthalmology screening
3. Consider T4/TSH if not done
4. If suspect seizures----EEG
5. Consider screening for Autism or a lang disorder

Close family hx of GDD: sibling, aunt, uncle, first cousin:
A. Known Cause: metabolic/genetic/structural CNS
B. Unexplained GDD

Are there features suggesting a specific diagnosis
A. Historical/physical findings/dysmorphic features suggesting Downs, Frag X, Rett, other genetic conditions or hypothyroidism.
B. History (Asphyxia)or physical findings (microcephaly, CP, focal findings) or seizures to suggest CNS injury or malformation?
C. Is there loss or regression of milestones, hx of consanguinity, prior unexplained child loss, or multiple miscarriages
D. Risk factors for environmental Lead exposure

Specific tests for that disorder
A. Specific tests for that disorder.
B. Cytogenetic tests, molecular genetics

If tests are (-)

Yes

MRI pref To CT Scan
Lead Screen

Comprehensive evaluation
1. MRI
2. Metabolic
3. EEG
4. Cytogenetics & referral

Stepwise: 1. MRI
2. Cytogenetics? Frag X
3. Metabolic
4. Refer
5. Subtelomeric /Rett
Expressive Speech Delay

- Common cause for concern
- ‘the child understands well but cannot verbalise’
- Detailed history and Clinical examination is key.
- Impt clues: Recurrent Childhood illness eg. URTI’s, middle ear infections, chronic hospitalisation, understimulation, language confusion.

- Approach: 1. Evaluate hearing + Tympanography
  2. Refer to ENT
  3. Refer to a speech therapist early
Developmental Language Disorders
Learning Disorders
Autism Spectrum Disorders
< 5% diagnostic yield

- Use resources carefully
- Avoid unnecessary testing
- Early referral
- Exclude hearing impairment
- Consider Fragile X testing especially in males on the Autism spectrum if positive family history, or clinical features (prev +- 2%)
Know When to stop Investigating!

- Overall yield for Global developmental delay: 40-70%
- A significant subset of patients where no cause is found.
- All families should be offered referral
- Counselling and assist with acceptance
- Genetic counselling for recurrence prediction.
- Strong evidence base for Early Intervention.
- Refer for therapy early....motivate for ongoing therapy.
- Optimise potential
- Focus on Quality of life for child and family
- Empower families: Support groups, information
- Prevent secondary disability
Conclusion

- Developmental Disability is common (10%) with concern about dev. being a common reason for presentation to a Paed.
- Surveillance and screening (high risk) must be done in the ‘medical home’
- There is no accepted evidence based guideline for investigating individual children.
- The History and Clinical examination must guide the clinician
- The evidence base for Early Childhood intervention is unambiguous!
In reality

- Unless the history and clinical examination provide insight into the diagnosis, early referral or consultation is advisable before embarking on costly undirected investigations.
References


5. Van Karnebeek et al: Diagnostic Investigations in Individuals with Mental Retardation; a systematic literature review of their usefulness: *European Journal of Human Genetics* 2005:13;6-25