Intellectual Disability

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Outline

- Definition
- Medical investigation
- Common syndromes
- Associated comorbidity and management
- Educational issues
- Medication
- Transition to adulthood

Definition

- Terminology differs across Western world
- Australia intellectual disability
- UK learning disabilities
- USA mental retardation (changed in DSM 5)

Cognitive Functioning
WHO 1968

- mild ID IQ 50-55 to 70
- moderate ID IQ 35-40 to 50-55
- severe ID IQ 20-25 to 35-40
- profound ID IQ below 20-25

Old terminology

- idiot- profound
- imbecile -moderate/severe
- moron or feeble minded- mild

Definition

- A significant impairment of cognitive and adaptive functions, with age of onset before 18 years.
- Usual presentation is with impairments in adaptive functioning.

DSM-IV and ICD-10

- **DSM IV**
- “dysfunction or impairment in >2 areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self direction, functional academic skills, work, leisure , health and safety”
- onset before age 18

DSM-1V and ICD-10

- **ICD-10**
- “mental retardation is a condition of arrested or incomplete development of the mind, which is especially characterised by impairment of skills manifested during the developmental period, contributing to the overall level of intelligence- cognitive, language, motor and social abilities”

Classification

- **DSM IV**
- Published 1995 text revision 2000
-
- vs

- **DSM -5**
- 10 years of revision released May 2013

DSM IV

- **Mental Retardation**
- A. Significantly subaverage intellectual functioning: an IQ of approximately 70 or below on an individually administered IQ test (for infants, a clinical judgment of significantly subaverage intellectual functioning).

DSM IV

- B. Concurrent deficits or impairments in present adaptive functioning (i.e., the person's effectiveness in meeting the standards expected for his or her age by his or her cultural group) in at least two of the following areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety.

DSM IV

- C. The onset is before age 18 years.
- *Code* based on degree of severity reflecting level of intellectual impairment:
- **317 Mild Mental Retardation:** IQ level 50–55 to approximately 70
- **318.0 Moderate Mental Retardation:** IQ level 35–40 to 50–55
- **318.1 Severe Mental Retardation:** IQ level 20–25 to 35–40
- **318.2 Profound Mental Retardation:** IQ level below 20 or 25

DSM 5

- **Intellectual Disability**
- A. Current intellectual deficits of two or more standard deviations below the population mean, which generally translates into performance in the lowest 3% of a person's age and cultural group, or an IQ of 70 or below. This should be measured with an individualized, standardized, culturally appropriate, psychometrically sound measure.

DSM 5

- B. And concurrent deficits in at least two domains of adaptive functioning of at least two or more standard deviations, which generally translates into performance in the lowest 3 % of a person's age and cultural group, or standard scores of 70 or below. This should be measured with individualized, standardized, culturally appropriate, psychometrically sound measures. Adaptive behavior domains typically include:

DSM 5

- Conceptual skills (communication, language, time, money, academic)
- Social skills (interpersonal skills, social responsibility, recreation, friendships)
- Practical skills (daily living skills, work, travel)

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DSM 5

- C. With onset during the developmental period.
-
- Code no longer based on IQ level

Tools to measure intelligence

- Under 5
- Generally use developmental tools which give a “mental age or developmental quotient”

Commonly used in Australia

- Bayley scales of Infant and Toddler Development (1 month-42 months)
- Griffiths Mental Developmental Scales (0-8 years)
- McCarthy Scales of Children's Abilities
- Stanford-Binet Intelligence Scales
- Mullen Scales of Early Learning

- WPPSI -Wechsler Preschool and Primary scale of Intelligence (2.6 to-7.3 years)

- WISC- Wechsler Intelligence Scale for Children (5-18 years)

Adaptive Functioning

- Refers to how effectively individuals cope with everyday life demands, and how well they meet standards of personal independence expected of someone of that age and socioeconomic and cultural background.

Adaptive functioning

- influenced by a number of factors
- motivation
- personality style
- education, social and vocational opportunities
- general medical conditions and mental disorders that co-exist with ID

Measures of adaptive functioning

- Is the instrument suitable to the ethnic and cultural background?
- Vineland -uses a number of different sources to gauge adaptive functioning

Frequency

- Occurs in 1-10 % of the population and is most accurately diagnosed in the school years.
- “Developmental delay” often used in preschool years
- sex ratio 1.5 :1 M:F
- biological inequity related to the sex chromosomes with the well established X-linked single gene mutations

Australian Institute Health and Welfare

- 2008 about half a million Australians had an intellectual disability (588,700)
- Most under 65 years.
- Biggest problems are severe communication problems in 60 %
- Self help and mobility issues are the other areas of difficulty

Frequency

- If we use the IQ construct then we assume it is a normally distributed trait in the general population and therefore 2 % of individuals would have an IQ less than 70.

- Most studies report rates of 1-2.5%

- In those with IQ's less than 50 the frequency is 0.3-0.5%

Demography

- Mild intellectual disability is associated with lower social class

- A much weaker association exists between social class in people with more severe ID

Aetiology

- WHY INVESTIGATE?
- 1. Diagnosis provides prediction
- 2. Often vigorously sought by the family
- 3. Helps establish accurate recurrence risk
- 4. Prevents expensive unnecessary and invasive investigations
- 5. Helps guide treatment and management

Diagnostic yield

- Significant improvement in yield over last 2 decades
- High frequency of the involvement of genes
- Most important studies include thorough physical examination
- Cytogenetics, neuroimaging and accurate EEG recording

Aetiology

- No longer true that the greatest yield is in those with more severe ID

- Due to newer diagnostic techniques in dysmorphology, cytogenetics and molecular genetics, neuroimaging and clinical neurophysiology yield is not dependent on degree of ID any longer

How to investigate

- Most patients lack specific findings on history or examination
- 1959 first time chromosomes could be seen down a microscope. Lejeune saw the extra chromosome 21 of Down syndrome
- 1960's banding became possible 3-4 % of patients with ID detected

- 1980’s
- FISH Fluorescein in situ hybridisation

- Led to diagnosis in 1990’s
- Microdeletion/duplication syndromes
- E.g. Di George
- Microdeletion syndromes defined

- 2000’s -simultaneous targeting subtelomeric (tip of chromosomes) very gene rich and some rare syndromes found

GENOMIC medicine

- Test for many genetic problems at the same time
- 2 techniques

- MICROARRAY on a glass slide millions of fragments of DNA then put patients DNA to find genetic variance
- NEXT GENERATION SEQUENCER can produce large amounts of genetic sequence for interpretation
- Aligns against reference genome from Human Genome Project

- Microarray has replaced microscope karyotyping now for paediatric practice

- Undiagnosed ID 10-15 % have a CNV

- Overall findings of large studies show a pick up rate of **5 -20%** of children with ID, multiple congenital abnormalities

Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

Am J Hum Genet. 2010 May 14; 86(5): 749–764

TABLE 2

COST of genome

- $100,000,000 in 2001
- $10,000 now technical cost of generating sequencing data but cost of interpreting data is unknown

EXOME Sequencing

- Exomes are becoming commercially available one panel looks at severe ID
- Can look at 50-100 genes at a time specifically
- We all have 50-100 de novo mutations

Microarray testing

- Microarray- based genomic copy number analysis
- Other names are
- Chromosomal Microarray (CMA)
- Molecular Karyotyping

CMA

- Includes

- array based comparative genomic hybridization (aCGH)
- Single nucleotide polymorphism (SNP)arrays

CMA

- G-banded karyotype

- Cytogeneticist visualizes and analyzes for chromosomal rearrangements including gains and losses

CMA

- Not standard in all clinical settings
- International Standard Cytogenomic Array Consortium (ISCA)
- 10 clinicians, 17 clinical laboratory geneticists, 9 genome scientists and bioinformatiticians
- Focused on clinical application of CMA

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- At present CMA is not recommended for prenatal testing although multicentre studies are underway

- Assessment of the pathogenicity of CNV

- G banded karyotyping detects <3 %
- CMA ~12.2%

- Most laboratories use a SNP or oligonucleotide array

Testing for ID and ASD

- Chromosomal Microarray can be
  - Normal
  - VOUS (variant of uncertain clinical significance)
  - Abnormal

VOUS

- Parental samples needed for clinical interpretation

AETIOLOGY

Prenatal

- Chromosomal; e.g. trisomy 21, fragile X syndrome and velocardiofacial syndrome (22q11-deletion syndrome).
- Genetic; e.g. tuberous sclerosis and metabolic disorders.
- Major structural anomalies of the brain.
- Syndromes; e.g. Williams, Prader–Willi, Rett.
- Infections; e.g. cytomegalovirus.
- Drugs; e.g. alcohol.

- In addition, children of low birth weight are at risk for intellectual disability: the lower the birth weight, the greater the risk.

Postnatal

- Head injury.
- Meningitis or encephalitis.
- Poisons e.g. lead.

Evolving Phenotype over Time

- Rett syndrome
- Prader Willi syndrome
- Angelman syndrome
- Velocadiofacial syndrome
- Williams syndrome
- Noonan syndrome
- Fragile X syndrome

History and physical examination

- detailed birth and prenatal history
- hereditary and family history
- three generation pedigree

Physical examination

- skin changes
- documentation of minor anomalies or abnormal findings by detailed description and measurement
- video monitoring of posture and gait or behaviour characteristics.
- serial evaluations over several years
- hearing and vision

Diagnosis-Genetics

- Imprinting may be cause of differential expression in conditions affecting same portion of genome e.g. Prader Willi and Angelman syndrome
- Trinucleotide repeat expansion is another mechanism e.g. Fragile X
- Rearrangement of subtelomeric regions recently implicated

Diagnosis-Genetics

- High resolution banding
- FISH(fluorescence in situ hybridisation)
- Subtelomeric analysis is important in moderate to severe ID
- These subtelomeric chromosome defects have been found in 6.5-7.4% of children with mod-severe ID

Diagnosis-Metabolic

- Metabolic testing should be focused
- Neonatal hypotonia, progressive coarsening of features, loss of skills, recurrent coma etc.
- Acid base
- Plasma and urine amino acids
- Lactate- blood CSF
- Organic acids
- Thyroid screen
- Cholesterol

Diagnosis-Metabolic

- Lysosomal enzyme analysis
- Plasma and urine carnitine analysis,
- Plasma VLCFA
- Extremely low yield for unselected metabolic screening

Neuroimaging

- consider especially in patients with
- microcephaly
- macrocephaly
- neurologic signs (spasticity, ataxia, dystonia, seizures, loss of psychomotor skills, abnormal reflexes)
- abnormal cranial contour

Neuroimaging

- CT for cranial synostosis or where intracranial calcification is likely (TS, intrauterine infection)
- MRI study of choice
- PET scanning
- may help date onset of problem (prenatal, perinatal, postnatal).

Environmental factors

- lead and methlylmercury poisoning
- alcohol
- thalidomide
- valproic acid
- polychlorinated biphenyls, dioxins, pesticides and tobacco smoke may be potential neurotoxins

Behavioural Phenotypes

- conditions with a known cause and a characteristic behavioural presentation

- Down , fragile X, 22q 11 deletion, Prader - Willi, Angelman's, Rett's, Smith- Magenis, foetal alcohol syndromes

- Individually rare but together 0.5% of child population

Down syndrome

- 1/600 live births closer to 1/1000 now
- 1/3 of all cases of severe and profound ID
- Smaller proportion of those with mild to moderate ID
- 1/3 psychiatric disorder
- 1/4 develop epilepsy in adulthood
- Many develop Alzheimer's in 40's

22q11 deletion syndrome

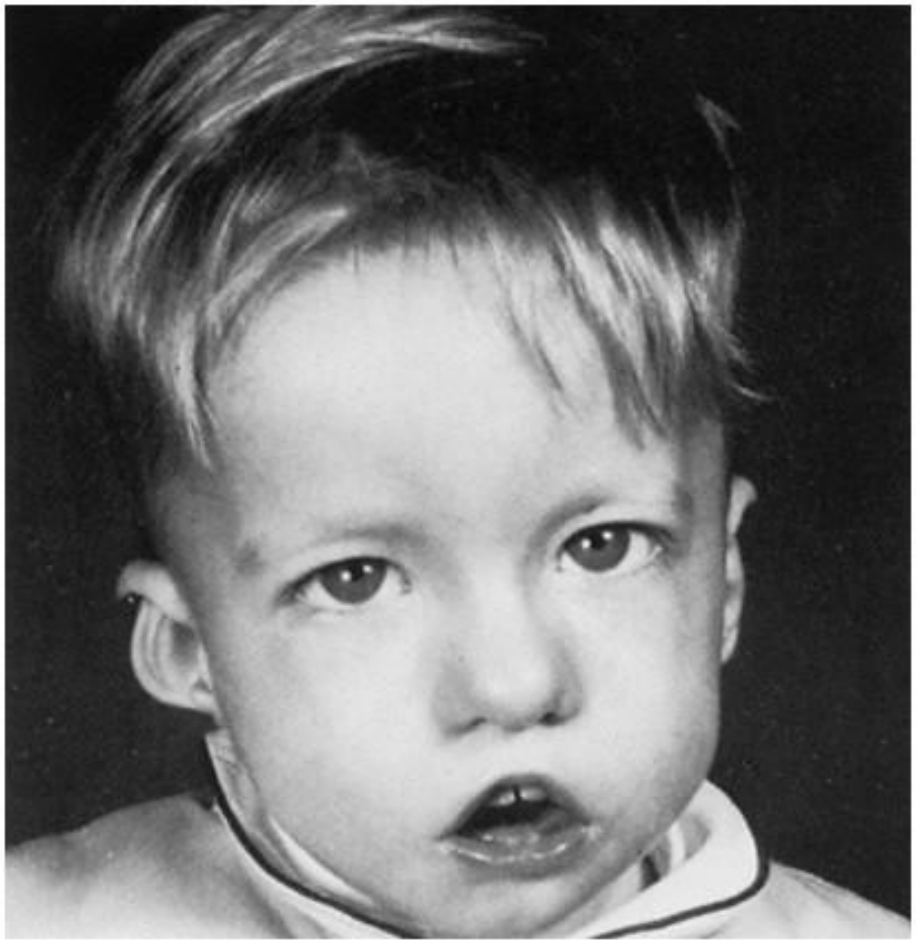
- 1/3000 or even 1/2000 children
- IQ can be normal and severe ID rare
- Attention deficits, nonverbal learning disability, lack of energy
- Autistic type features
- Abnormal brain changes on MRI

22q11 deletion syndrome

- 85% cases have submicroscopic deletion at 22q11.2.
- Wide phenotypic expression
- 180 associated anomalies
- facial dysmorphism
- congenital heart disease
- hypotonia and immune disorders

22q11 deletion syndrome

- hypernasal speech is due to submucous cleft palate
- velopharyngeal insufficiency or cleft palate
- infections of respiratory tract and ear due to partial or total absence of the thymus gland
- Fits - check calcium levels because of aberrant functioning if the parathyroid glands



Fragile X syndrome

- third most common 1/3000
- distal part of the long arm of X chromosome
- trinucleotide repeat expansion
- apart from ID, boys have more deficits in motors skills, autistic features, social anxiety, tangential language, hyperactivity, attentional difficulties

Fragile X syndrome

- hypersensitivity to sensory stimuli and social stimuli
- inhibitory control deficits
- macroorchidism (100 mls) only past puberty
- girls with fragile X have fewer problems

Fragile X syndrome

- Scoring system of 6 historical/clinical characteristics
- ID, family history, elongated face, large or prominent ears, attention deficit hyperactivity and autistic-like behaviour
- if we only test those with 5 out of 6 then 60 % of testing could be eliminated without missing positive cases

Fragile X syndrome

- laboratory confirmation is relatively inexpensive
- molecular analysis of the FMR1 gene
- normal CGG repeat segments <50
- premutations 50-230 repeats
- full mutations >230 repeats

Fragile X syndrome

- deletions and point mutations of the FMR1 are rare but should be looked for in persons with characteristic phenotypes and normal CGG repeat analysis
- Other fragile sites FRAXE may be found using cytogenetic and molecular studies
- Test anyone with unexplained ID especially with family history

Prader-Willi syndrome

- loss of the paternal contribution of the proximal portion of the long arm of chromosome 15 (deletion or maternal disomy or imprinting of 15q11-13)
- high incidence of ID
- obsessive, repetitive activities
- mood instability, self mutilation

Prader- Willi syndrome

- 1/10,000
- hypotonia, failure to thrive, delayed sexual development, scoliosis, acromicria, small stature and persistent skin picking
- Flat face prominent forehead with bitemporal narrowing and almond shaped eyes with triangular mouth

Prader-Willi

- first 6 months
- hypotonia, feeding difficulties, sleepiness
- 1-4 years hyperphagia develops due to hypothalamic abnormalities
- hypotonia improves
- most important issue is dietary management
- medication, GH, behavioural approach

Prader Willi syndrome

Prader Willi syndrome

Angelman syndrome

- caused by loss of maternal contribution to proximal portion of long arm of chromosome 15
- no speech, jerky movements, happy demeanour (100%),
- epilepsy (>80%)
- obsessions, compulsions, overactivity, eating and sleeping difficulties
- 50% have episodes of inappropriate laughter

Angelman Syndrome

Angleman syndrome

- Most 68% are deletions of UBE3A
- Maternal UBE3A is deleted due to repetitive DNA elements causing chromosome alignment errors
- 13% are intragenic mutations disrupt protein function
- 6 % are imprinting centre defect
- 3 % are uniparental disomy

- 1997 UBE3A gene was discovered
- 10 years after the chromosomal deletion was identified
- Rare 1 in 10-20,000

Rett syndrome

- 1/10,000 females
- rarely occurs in males
- distal arm of Xq28 75% due to mutation of MECP2 gene
- normal development until 6-18 months
- deceleration of head growth

Rett Syndrome

- inability to walk
- ataxic movements of torso and limbs
- rate of regression is variable months
- regression is followed by a period of stabilisation then re-emergence of skills
- hyperventilation and breath holding
- facial grimacing and hand ringing

Rett syndrome

- Loss of purposeful hand movements with stereotypic movements
- Loss of verbal skills
- All lead to loss of function, physical (scoliosis and leg deformities), social, linguistic and adaptive behaviours

Foetal alcohol syndrome

- Neuronal apoptosis may be triggered in the last trimester and this may be sensitive time for the effects of ethyl alcohol (intrauterine synaptogenic phase)
- Studies of 10 -12 year old boys, show those whose parents with alcohol and drug abuse have a higher rate of ID than a control group

Foetal alcohol syndrome

- Longitudinal studies of mothers with a history of alcohol abuse in pregnancy show a trend towards a dose response relationship between level and length of exposure to alcohol and intellectual disability and behaviour problems
- Smoking and alcohol in pregnancy associated with ADHD

FAS

Prematurity

- Birthweight < 1000g risk factor for ID
- Most survivors of 22-26 weeks will be free of a major disability although 20% will have ID diagnosed later
- 40-50% will develop neurodevelopmental and neuropsychiatric problems in childhood and teenage years

Infections

- Meningitis and encephalitis in early infancy and childhood still cause ID although the outcomes are much better now
- Intrauterine CMV, toxoplasmosis and rubella continue to cause ID
- Measles and SSPE

Traumatic brain injury

- Increases the risk of intellectual disability
- American study showed that exposure to violence and trauma related psychological distress showed a decrease in IQ of 7.5 points and a reduction in reading achievement by 10 points

Chemicals

- Radiotherapy, chemotherapy and intrathecal corticosteroids all implicated in ID
- Prenatally exposed survivors of Hiroshima and Nagasaki showed the critical time was 8th-15th week of gestation and the increase in prevalence of ID was linearly dose related

Medical Problems

- Increased rate of medical problems
- Epilepsy 14-44% higher in more severe ID
- Combination of ID and epilepsy is a strong predictor of psychiatric and behavioural problems
- Hypothyroidism is common in Down syndrome

Medical problems

- Stomach cancer, and cancer of gall bladder, oesophagus, testis, thyroid and connective tissue all occur with greater frequency
- Visual problems 10 times more common cataract and keratoconus also common
- Hearing problems 40 times more common
- In one study of institutionalised people with IQ<50 69% had constipation

Psychiatric disorders

- Over represented in ID population
- As IQ decreases, these increase
- Psychotic conditions, pica, self- injurious behaviours, stereotypies and ADHD symptoms common

Psychiatric disorders

- In Australia, estimated that 57% of people aged under 65 years with intellectual disability also had psychiatric disability

Psychiatric disorders

- Schizophrenia over-represented
- 4.4% vs 0.4% in general population
- similar rates in autism
- other psychiatric disorders are at least as common in an adult population of people with ID as general community sample

Forensic issues

- Low verbal IQ associated with increased risk of conviction for violent crimes not accounted for by socioeconomic or educational status
- most common crimes are child sexual abuse and arson
- also those with ID are at greater risk of violence and sexual abuse

Treatment and intervention

- Psychosocial, psychological and educational treatment help with overall adjustment and behaviour in deprived children with low IQ
- possibly may increase IQ as well
- Behavioural methods for self injury appear to be best if used systematically by well trained people

Psychotropic Medication

- Recent Cochrane review
- 8 randomised controlled trials showed no evidence of whether antipsychotics helped or harmed adults with ID and challenging behaviours

Risperidone

- American study 2002
- double blind randomised controlled
- using risperidone for disruptive behaviours in 118 children with ID aged 5-12 years
- good benefit and few side effects (slight weight gain)
- another small study showed sedation and weight gain were greater problems

Psychotropic Medication

- Other drugs include naltrexone, mood stabilisers, serotonergic
- Antiepileptics sometimes helpful although one study using valproic acid in a group with ID and epileptiform discharges on EEG, showed a deterioration in memory and increased internalising behaviours

Transition to adult services

- Poor in Australia
- Adult psychiatrists see some children with ADHD to continue medication
- No specialty in adult psychiatry of intellectual disability unlike UK model
- Very few public outpatients
- Private psychiatrists

Education

- 45% of students with intellectual disability attended ordinary school classes, compared to 95% of students with physical or diverse disability.

Workforce

- In 2003, the labour force participation rate of those aged in their 20s was around 60%
- for those aged in their 30s between 34% and 46%
- Well below the 85% participation by young adults without disability

Societal attitudes

- 200 years ago these children were often left to die
- Early 20th century eugenics movement suggested sterilisation to prevent spreading of genes to future generations
- Last 25 years more respect given to rights of people with ID