Down syndrome

Down syndrome is a congenital disorder resulting from an extra copy (trisomy) of chromosome 21. The mechanisms by which increased dosage of genes on chromosome 21 leads to Down syndrome are as yet unknown. However, neuropathological changes associated with dementia in Down syndrome are typical of Alzheimer's disease.

Epidemiology

- Incidence: 1/650-1/1000
- All ethnic groups
- Male = Female

Genetics

Trisomy 21 can occur due to the following mechanisms:

- Chromosome 21 non-disjunction (see section 9.1) [95%]. The risk of chromosome non-disjunction increases with advancing maternal age:
  At 18 years of age the risk is 1:1500
  At 38 years of age the risk is 1:150
- Robertsonian translocation (involving chromosomes 13, 14, 15, 21 or 22) [2%]. Fifty percent are familial.
- Mosaicism, e.g. post-zygotic non-disjunction [2%]
- Other chromosome rearrangements [1%]

Clinical Presentation

Clinical features are variable. Trisomy 21 may present pre- or post-natally.

Pre-natal:

- Miscarriage
- Abnormal maternal serum screening, increased hCG, inhibin-A.
- Ultrasound scanning: increased nuchal translucency, nasal bone hypoplasia, cardiac defect, double stomach bubble (secondary to duodenal atresia).

Post-natal:

- Hypotonia and feeding problems in infancy
- Dysmorphism
- Congenital anomalies, particularly congenital heart defects

Physical Signs

- Dysmorphism
- Upslanting palpebral fissures, epicanthic folds, Brushfield spots
- Protruding tongue
- Brachycephaly
- Single palmar creases, clinodactyly, sandal gap
- Evidence of congenital heart defect
- Evidence of gastrointestinal obstruction

Diagnosis

- Routine karyotyping is essential to determine the aetiology. Only need parental karyotype if the child has a chromosomal rearrangement causing trisomy 21. Pre-natal cytogenetic testing is available.
- Skin biopsy if mosaic Down syndrome suspected
- Echocardiogram
- Thyroid function

Complications

- Congenital heart defects (40-50%), VSD is the most common, followed by AVSD, ASD, PDA and Tetralogy of Fallot.
- Short stature
- Hypothyroidism (20-40%)
- Diabetes mellitus (1%)
- Leukaemia, especially ALL (2%)
- Obstructive sleep apnoea
- Duodenal atresia/ stenosis, hirschsprung disease
- Behavioural problems (10%)
- Seizures (8%)
- Dementia, mean age 50yrs+
- Atlantoaxial subluxation (15% on X-ray, few symptomatic)
- Eyes (refractive errors)
- Learning difficulties, average IQ 45-48, adults will require daily supervision.

Life expectancy:

- Median age at death is 49 yrs.
- Congenital heart disease major factor in increased mortality.

Treatment

- Will depend on time of presentation and specific complications.
- Surgical correction for congenital heart and gastrointestinal defects
- Referral to local child development centre

Genetic Counselling:

- Recurrence risks (RR) depend on the cause of trisomy 21:
  For Non-disjunction: Women aged <39yrs RR= 0.8%; for women aged >39yrs RR is age-related risk
- After 2 pregnancies with trisomy 21, there is approx 10% recurrence risk, consider parental mosaicism
- Robertsonian translocation: if *de novo* the recurrence risk is low; if inherited the recurrence risk is up to 50%

References

Roizen NJ, Patterson D. Down syndrome. Lancet 2003; 361:1281-9.

Face
Diagram of Fallots tetraology
Karyotype tri 21
Nuchal thickening
Palmar creases