Wolf-Hirschhorn Syndrome

**Synonyms:** chromosome 4p deletion syndrome, 4p- syndrome, monosomy 4p syndrome

Wolf-Hirschhorn syndrome (WHS) is characterised by learning difficulties, epilepsy, growth delay and craniofacial dysgenesis.\(^1\)

**Epidemiology**
- The incidence is estimated at 1 in 50,000 births.\(^2\)
- Female-to-male ratio is 2:1.

**Genetics**

WHS occurs due to partial deletion of the short arm of chromosome 4 (4p-).\(^3\) About half of patients have a de novo pure deletion of 4p16 and about 40-45% have an unbalanced translocation with both a deletion of 4p and a partial trisomy of a different chromosome arm.\(^4\) These unbalanced translocations may be de novo or inherited from a parent with a balanced rearrangement. The remainder have other complex rearrangements leading to a 4p16.3 deletion.

**Presentation**\(^5,6\)
- Severe growth restriction, microcephaly, hydrocephalus, corpus callosum agenesis.
- Severe general learning disability, severe limitation of comprehension and speech, seizures, ataxic gait, hypotonia, muscle hypertrophy.
- Microcephaly, a distinct 'Greek warrior helmet' face with characteristic broad-beaked nose, high frontal hairline and frontal bossing.
- Contracture of hands, wrists and feet.
- Poor development of secondary sexual characteristics.
- Closure defects (cleft lip or palate, coloboma of the eye, cardiac septal defects).
- Hypoplasia of the kidneys and genital tract. Diaphragmatic hernia with secondary lung hypoplasia.
- Immunodeficiency.

**Differential diagnosis**
- Similar multiple congenital anomalies and intellectual developmental disorders, including proximal 4p syndrome and Seckel's syndrome.

**Investigations**

- **Prenatal diagnosis:**
  - Anomaly ultrasound scan will suggest distinct physical characteristics and should be followed by karyotyping.\(^7\)
  - Chromosomal analysis from amniocentesis or chorionic villus sampling.
  - Umbilical blood sampling for rapid fetal karyotyping.

  - Immunoglobulin and T-cell numbers and function for likely immunodeficiency.
  - Electroencephalography (EEG): characterised by distinctive seizure and EEG patterns.\(^3\)
  - Echocardiography: possible atrial septal defect or ventricular septal defect.
  - Imaging of the urinary tract.
  - MRI and CT scans for underlying brain pathology - eg, agenesis of the corpus callosum and enlarged ventricles.

**Management**
- No treatment exists for the underlying disorder and management is supportive.
- Seizures may be difficult to control.
- The management plan will require a multidisciplinary team approach and depend on the range of associated developmental, physical and behavioural problems.

**Prognosis**
- Frequently results in stillbirth or death within the first year.
- If patients survive beyond infancy, they have slow but constant progress in terms of development.
- About one third die within the first two years of life, usually due to a heart defect, aspiration pneumonia, other severe infection or resulting from a seizure.
- Recurrence risk is negligible unless a parent is a translocation carrier.
Prevention

Genetic counselling will assess the risk to family members, based on the mechanism of origin of the deletion. Prenatal testing is possible where one parent is known to be a carrier of the condition.\[6\]

Further reading & references

4. Wolf-Hirschhorn Syndrome, WHS; Online Mendelian Inheritance in Man (OMIM)

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