

Anaesthesia and *Wolf-Hirschhorn Syndrome*

Bösenberg AT

Department of Anaesthesia, University of Cape Town, South Africa

Correspondence to: Prof A Bösenberg, E-mail: Adrian.Bosenberg@uct.ac.za

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CASE REPORT

A 4-year-old female, weighing 12kg, presented for ENT and dental examination under anaesthesia. Nasal intubation was requested to facilitate the dental examination. On examination she had the distinctive facial features of Wolf-Hirschhorn syndrome that included hypertelorism, prominent glabella, short "beaked" nose, short philtrum, mild micrognathia and microsomia, but she had no cleft lip or palate, nor iris coloboma. She had generalised hypotonia. She initially failed to thrive because of feeding difficulty, recurrent infections and aspiration pneumonia, requiring numerous hospital admissions. She is developmentally delayed and has a history of convulsions that are controlled with levetiracetam 750mg and lamotrigine 25mg. The PDA noted at birth had closed by 3 months and there was no other cardiac abnormality. She had intra-uterine growth retardation (IUGR) and was delivered prematurely at 34 weeks by emergency Caesarean section to a 34-year old primigravida.

At 8 months she underwent an anti-reflux procedure for recurrent aspiration. A feeding gastrostomy was placed at the same time, in view of her difficulty with swallowing and refusal to eat. The Nissen fundoplication was made difficult by a small diaphragmatic hernia. Intubation at that time was noted to be difficult, but not impossible, using a Miller 1 laryngoscope blade. Anaesthesia was uneventful and consisted of a sevoflurane induction, maintenance with isoflurane and a thoracic epidural for peri-operative pain management. There was no suggestion of malignant hyperthermia.

On this occasion she required no sedative premedication. On arrival in theatre, she was asleep in her father's arms and a "steal induction" using sevoflurane was performed. After ascertaining that the larynx could be visualised, albeit with some difficulty, a nasal RAE endotracheal tube was softened in hot water to facilitate passage through the more patent left nostril. A smaller ET tube (4mm) than expected for her age (5mm) was placed atraumatically without muscle relaxants. A throat pack was inserted to prevent potential soiling of the airway. Anaesthesia, lasting 2 hours, was uneventful and she remained normothermic. A paracetamol suppository (250mg), placed prior to surgery, provided adequate postoperative analgesia.

Introduction

Wolf-Hirschhorn syndrome (WHS), or alternatively 4p- deletion syndrome, was first documented by Henry Cooper and Kurt Hirschhorn in 1961¹ Wolf and Hirschhorn subsequently published their findings in the same edition of the journal *Humangenetik*, bringing the syndrome to the attention of geneticists and other health care professionals in 1965. WHS has a prevalence of 1:50000 births in the USA, with a 2:1 female preponderance.²⁻⁴ However, recent reviews suggest that WHS may be more common than was previously thought.^{2, 3}

Deletion is when part of the chromosome is missing. WHS is the consequence of deletion of genetic material of different sizes at varying breakpoints on the short arm of the chromosome 4. The critical region for determining the WHS phenotype is 4p16.3. Clinical presentation varies widely, in keeping with the amount of genetic material deleted, and is characterized by a variety of midline fusion defects.

About 87% of cases represent a de novo deletion, of which 80% are paternally derived, while about 13% are inherited from a

parent with a chromosome translocation. The risk of future inheritance depends on the origin of the deletion, and prenatal testing can be offered to determine this. The majority (60%) of these chromosomal defects can be detected using routine G-banded cytogenetic analysis; the remainder with FISH (Fluorescent *in situ* hybridisation) analysis.

Genetic analysis can predict the prognosis with relative certainty. The crude infant mortality is 17%, and up to 30% in the first 2 years.² This mortality is probably an underestimation, given that many die before diagnosis is made or even suspected. The usual cause of death is aspiration pneumonia, infection, or seizures. Genetic analysis can also assist families to decide on the most appropriate health maintenance and education programme, or to be referred to a WHS support group.⁴

Clinical features

The diagnosis of WHS is suggested by the characteristic facial appearance, growth delay, psychomotor retardation, and seizures (Table 1) and is confirmed by cytogenetic analysis.

Table 1: Typical clinical features of WHS and their incidence.²⁻⁴ Those marked with an asterisk are not present, nor yet demonstrated in this patient

Clinical feature			
Incidence >75%	50-75%	25-50%	<25%
Facial features	*Skin changes	Hearing defect	Other anomalies of
“Greek helmet”	Skeletal abnormality	*Cardiac defects	*Liver
Growth retardation	*CF asymmetry	Eye; optic n defect	*Gallbladder
Mental retardation	Ptoxis	*Cleft lip palate	Gut
Hypotonia	Abnormal teeth	GU tract defects	Diaphragm
Less muscle bulk	Ab deficiency IgA	CNS defects	Oesophagus
Seizures		Stereotypes:	*Lung
Typical EEG		Hand washing	*Aorta
Feeding difficulties		Hand flapping	
		Rocking	

The typical *craniofacial features*³⁻⁶ include microcephaly, high forehead with prominent glabella extending into the broad bridge of a beaked nose, ocular hypertelorism, epicanthic folds, prominent eyebrows, short philtrum, a small down-turned fish-like mouth, micrognathia, and poorly formed ears. These craniofacial features are imaginatively described as a “Greek warrior’s helmet” appearance.^{3, 6} These features can even be diagnosed antenatally using three-dimensional ultrasound.⁶

All affected individuals have intra-uterine *growth retardation* as well as slow post-natal weight gain. Achieving adequate nutrition is difficult, considering their difficulty in sucking and poorly coordinated swallowing (hypotonia). Most require special feeding techniques, gavage feeding or a feeding gastrostomy. They remain short in stature despite adequate protein and calorie intake.

Gastroesophageal reflux with consequent aspiration may further contribute to the failure to thrive. An anti-reflux procedure is advocated to reduce the risk of aspiration, and chronic respiratory problems, and to improve nutrition.

Seizures are common, and present in early infancy with a peak incidence around 9-10 months.⁷ These may be clonic, tonic-clonic, atypical absences or myoclonic in nature and are frequently triggered by fever. Status epilepticus occurs in the majority of individuals.⁷ Atypical absences develop between age one and five years in more than 60% of children. Seizures can be difficult to control in some during the early years, but if properly treated tend to disappear with age.⁷ Distinctive electroencephalographic (EEG) abnormalities, not necessarily associated with seizures, have been found in 70% of individuals with WHS.⁷

Seizure activity may be controlled with valproic acid alone, or in association with ethosuximide when absence seizures are present. Alternative agents include phenytoin, carbamazepine, lamotrigine and levetiracetam. Along with other side effects, anti-epileptic agents may cause skin lesions, (including Steven-Johnson syndrome), liver dysfunction, (including the risk of liver failure), renal dysfunction, bone marrow depression or platelet dysfunction.

Mental retardation in WHS was previously considered to be universally severe and these children were described as “mere

survivors devoid of personality” because of their inability to speak or develop communication skills. Recently Battaglia et al⁴ revealed that a spectrum of intellectual ability ranging from a mild degree of retardation (8%), moderate (25%), to severe in the majority (67%) can be found. Behavioural stereotypes (holding the hands in front of the face, hand-washing or flapping, patting self on chest, rocking, head-shaking, leg stretching) are common. Expressive language, usually limited to guttural or disyllabic sounds is at the level of simple sentences in 6%. Comprehension is also limited. *Hearing loss* (over 40%), mostly of the conductive type, compounds the problem.

Structural *brain abnormalities* occur in about one third of individuals with WHS. These include an absence or thinning of the corpus callosum; a hypoplastic brain with narrow gyri, arhinencephaly, absence of olfactory bulbs and tracts, and marked hypoplasia of the cerebellum.⁴

All have *delayed milestones* to a variable degree. *Hypotonia* with muscle under-development, particularly in the lower limbs, compounds the developmental delay. Approximately only 45% learn to walk (independently (25%) or with support (20%)) albeit by as late as 12years.⁴ Only 10% achieve sphincter control by day, usually between ages eight and 14 years.⁴ About 30% of children reach some autonomy with eating (10% self-feed), dressing (20%), and simple household tasks. More advanced milestones can be reached with appropriate stimulation.

Other anomalies that may require surgery or may have an impact on the anaesthetic management are described.⁸ *Skeletal anomalies* that include malformed vertebral bodies that may lead to kyphosis/scoliosis, accessory or fused ribs, hip dysplasia and clubfeet are seen in about 60%. Radiological bone age is delayed. *Congenital cardiac defects* (50%) are usually not complex. The most frequent are atrial septal defects (27%), followed by pulmonary stenosis, ventricular septal defects, patent ductus arteriosus, aortic insufficiency, and tetralogy of Fallot.⁴ *Pulmonary isomerism* and congenital diaphragmatic hernia have been described. Recurrent respiratory infections are common - secondary to aspiration or IgA deficiency. *Otitis media*, in addition to the congenital abnormalities of the middle and inner ear⁹, may require surgery to prevent further hearing impairment. (See Figure 1 for external ear anomalies)

Figure 1: Ear anomalies are common. The ear is poorly formed with a tiny external auditory meatus.



Figure 2: Dental anomalies are common. Notice the poorly formed deciduous teeth and the fused right lower incisor



Dental hygiene may be difficult to maintain. In addition, a variety of dental problems (50% cases) may be encountered. These include delayed eruption and subsequent persistence of deciduous teeth, agenesis of some permanent teeth, taurodontism (variation in tooth form) in the primary dentition, peg-shaped teeth, and fusion of teeth.^{3,4} (See Figure 2).

Urinary tract malformations (25%) include renal agenesis, renal hypoplasia, horseshoe kidney, renal malrotation, bladder extrophy, or obstructive uropathy.⁴ Some of these can be associated with vesicoureteral reflux.¹⁰ Hypospadias and cryptorchidism occurs in 50% of males; absent uterus and streak gonads have been reported in females.^{3,10}

A variety of *ophthalmologic* problems may also need surgical management. These include nasolacrimal obstruction, glaucoma, exodeviation eye (See Figure 3) optic nerve coloboma, and foveal hypoplasia.^{3,11,12} Eyelid hypoplasia, requiring skin grafting, has occasionally been observed.³

Antibody deficiencies occur in two thirds of WHS and are responsible for the recurrent respiratory tract infections and otitis media seen in these children. The deficiencies may be either an isolated IgA deficiency; IgA or IgG2 subclass deficiency, or impaired polysaccharide responsiveness.¹³

Figure 3: Typical facial features of WHS include microcephaly, prominent glabella, broad nasal bridge, ocular hypertelorism, epicanthic folds, short philtrum, micrognathia and a small downturned fish-like mouth.*



*Photos published with parental permission

Anaesthetic considerations

Despite two recent publications in the paediatric anaesthetic literature,^{14, 15} knowledge of the anaesthetic implications of WHS is limited. There are a number of challenges that the anaesthesiologist may face for a variety of surgical procedures.

Firstly, communication may be particularly difficult in view of the mental retardation, hearing defect and poor eyesight. The parents are often widely read and their input may prove invaluable - particularly in an emergency.

The airway should be carefully evaluated in view of the cranio-facial abnormalities. Micrognathia, microsomia and a web neck may contrive to make direct laryngoscopy difficult, although usually not impossible.^{14, 15} Stable fixation of the endotracheal tube may be difficult in the presence of oro-facial clefts.¹⁶ In view of the growth retardation, smaller endotracheal tubes and airway equipment may be required¹³ as in our patient. Careful planning is essential.

Pulmonary function may be compromised, but pulmonary function testing requiring patient cooperation is virtually impossible. Clinical assessment, chest x-ray and blood gas analysis may be the only option. Smaller doses of muscle relaxants should be used in view of the hypotonia.

Neuraxial blockade, including caudal blockade, may be challenging. Coagulation defects, secondary to some anti-convulsants must be excluded. The sacral dimple may preclude the use of a caudal unless an ultrasound is available to exclude an occult spina bifida or other abnormality. Kyphoscoliosis may preclude the use of an epidural except in experienced hands.

Prophylactic antibiotics will be required for those with congenital cardiac defects. Careful assessment including echocardiography, may be warranted when cardiac function is compromised, or kyphoscoliosis makes assessment difficult.

Anti-convulsive therapy should be continued peri-operatively. A history of seizures may dictate the use of non-epileptogenic anaesthetic agents. Sevoflurane can trigger convulsions, and epileptiform EEG patterns have been described with its use, and should theoretically be avoided. It was not a problem in this patient. Other pharmacological considerations include the effect of anticonvulsants on the liver, drug metabolism and clotting function.

Malignant hyperthermia (MH) has been described in two cases^{17, 18} one with a delayed onset¹⁸, but the risk has been refuted by others.^{19, 20} It seems highly unlikely that WHS is associated with MH. Despite the generalized hypotonia, the muscle per se is not involved, nor is the ryanodine receptor.

Conclusion

Wolf-Hirschhorn syndrome is a typical example of a chromosomal deletion syndrome. A variable amount of chromosome material from the short arm of chromosome 4 may be deleted but must include the critical region of 4p16.3 for the typical WHS phenotype to be expressed. Deletion of additional chromosomal material will affect their clinical appearance and presentation, to a greater or lesser extent.

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