

Williams syndrome: an update on clinical and molecular aspects

Williams syndrome is a neurodevelopmental disorder associated with a characteristic physical and behavioural phenotype. The syndrome was described in 1961 by Williams *et al* who recognised a group of children with supravalvular aortic stenosis, mental retardation, and dysmorphic facial features.¹ Beuren *et al* independently described the syndrome, noting also the friendly nature of these children, and later expanded it to include dental anomalies and peripheral pulmonary artery stenosis.^{2,3} Subsequent authors recognised the association with idiopathic hypercalcaemia.

Since the discovery in 1993⁴ that Williams syndrome is caused by a chromosomal microdeletion, features resulting from the deletion of contiguous genes, there has been increasing interest in trying to unravel the underlying molecular basis of the cognitive and behavioural aspects of this syndrome.

Clinical history

Infants with Williams syndrome are usually born following an uneventful pregnancy with an average birth weight of 2760 g. In the neonatal period feeding problems are common and often accompanied by vomiting and poor weight gain. Frequent crying, sleeping problems, and constipation are also frequently reported by parents, and rectal prolapse occurs in around 10% of cases. Hernias, most commonly inguinal, occur in over a third of cases. A proportion of infants are found to have idiopathic hypercalcaemia, which is treated with a low calcium and vitamin D restricted diet. The underlying hormonal basis for the hypercalcaemia is not known, although there is a delayed calcitonin response to a calcium load on testing. Resolution of hypercalcaemia occurs spontaneously, usually at around 18–24 months of age.

Developmental milestones are delayed with sitting unsupported achieved at an average of 13 months and walking at 28 months. Later, difficulties in walking on uneven ground or descending stairs appear to result from defective three dimensional visual perception. After an initial period of speech delay most children with Williams syndrome tend to be overtalkative with a characteristically hoarse voice. This, with a notable overfriendliness towards strangers, has sometimes been termed a “cocktail party manner”.

Hypersensitivity to certain sounds, particularly electrical appliances such as drills and vacuum cleaners, fireworks or balloons popping, affects over 90% of individuals and appears to be centrally mediated. This hyperacusis, or the ability to cope with it, tends to improve with age.

Full scale intelligence quotient (IQ) is usually in the 50s to 60s (range 40–85), although this camouflages a very uneven cognitive profile. People with Williams syndrome have relatively good verbal abilities and auditory rote memory with deficient visuospatial abilities^{5,6} and this has been termed the Williams syndrome cognitive profile (WSCP).^{7,8} While many develop quite good reading ability, few have more than very elementary numeracy.

Physical phenotype

Facial features are very characteristic: a retrousse nose with flat nasal bridge and bulbous upturned tip, a wide mouth with full lower lip, flat malar region with full cheeks, periorbital fullness, medial eyebrow flare, epicanthic folds and

often stellate irides (fig 1). With age the face becomes thinner and coarser, and loss of subcutaneous tissue can lead to a “scraggy” appearance. The primary teeth are small, irregular, and widely spaced although in adulthood teeth tend to be crowded. Hair is usually curly and premature greying occurs in 60% of adults. The neck is long, with a prominent hyoid often apparent in adults. A characteristic posture with sloping shoulders, exaggerated lumbar lordosis, and flexion at the knees and hips may be seen. The hands are small with relatively short fingers. Squints and refractive errors are common, occurring in around 40% of patients.

There is postnatal growth retardation, with most children below the 10th centile for height. In the study by Martin *et al*, mean adult height was 159 cm for men and 147 cm for women.⁹ Failure to thrive and slim build in childhood often gives way to relative obesity in adults, with a characteristic “Hottentot” pattern of fat distribution, particularly in women. Several studies, backed by a wealth of anecdotal evidence, have demonstrated an earlier onset of puberty in Williams syndrome compared to the general population. Precocious puberty has been described in one case.^{9A}

Behavioural phenotype

Poor concentration and distractibility are almost universal. Most children with Williams syndrome have poor relationships with their peers, seeking instead adult company. They tend to be outgoing, talkative, and socially uninhibited, and have high rates of preoccupations and obsessions with objects, people, and activities. Excessive anxiety about health issues and in anticipation of events is typical, as is emotional lability. Most are described by their families as friendly, caring, and attentive to the feelings of others. Aggressive behaviour is less common.

Natural history

General health is usually good. Cardiovascular abnormalities occur in around 75% of cases. The characteristic abnormalities are supravalvular aortic stenosis and peripheral pulmonary artery stenosis, although valvar and septal defects occur less commonly. Hypertension occurs in around one third of patients, and ongoing medical surveillance should include blood pressure monitoring. Renal artery stenosis has been described and cerebral and coronary artery stenoses have led to cerebrovascular accident and sudden death from myocardial infarction in some cases.

Urological abnormalities, both structural and functional, are seen with increased frequency in Williams syndrome. Nephrocalcinosis occurs secondary to hypercalcaemia and renal function may decline with age.

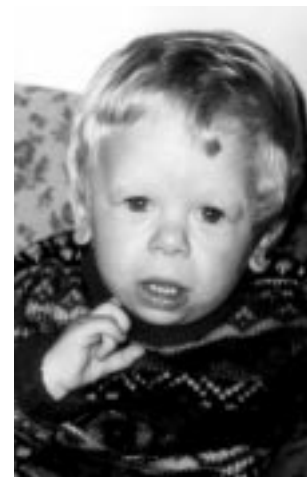


Figure 1 Typical facial appearance in Williams syndrome.

Individuals with Williams syndrome tend to adopt a typical posture with sloping narrow rounded shoulders and flexion at the hips and knees. Scoliosis is seen in around 17%, large joint contractures in around 15%, radioulnar synostosis in 10%, and recurrent patellar dislocation in 5% of cases (Metcalf K, unpublished data, 1998).

Most acquire independence in toileting, dressing, and washing although supervision is often needed, and very few are able to cook independently or look after finances. They continue to require substantial supervision and support in adulthood and most remain at home, in residential or in sheltered accommodation.¹⁰

Genetics

Williams syndrome usually occurs as a sporadic new dominant condition, although parent-child transmission has been reported.^{11 12} As expected, there is concordance for the condition in monozygous twins and discordance in dizygous twins.

The cause is known to be the presence of a submicroscopic chromosomal deletion on one of the number 7 chromosome pair at 7q11.23. Routine chromosome analysis is usually normal and the deletion is detected by fluorescent in situ hybridisation (FISH) using a probe for the elastin gene.^{13 14} Molecular studies have shown the microdeletion to encompass approximately 2 cM (1.4 Mbases) of genomic DNA, the breakpoints lying approximately 1 cM either side of the elastin gene.¹⁵ There appears to be little variability in the size of the deletion between Williams syndrome patients, as determined by polymorphic markers, despite the phenotypic variability between them. Deletions on the maternally and paternally inherited chromosomes occur with equal frequency and there does not seem to be a parental age effect. Meiotic recombination between polymorphic markers proximal and distal to the deletion has been documented, suggesting that unequal crossing over between homologous regions is the mutational mechanism in most cases.^{16 17} However, the absence of recombination in other families suggests that intrachromosomal rearrangements may also occur. The presence of a genomic duplication at the deletion breakpoints may act as a hotspot for the recombination events causing Williams syndrome.

While deletion of the elastin gene in Williams syndrome can cause supravalvular aortic stenosis and other cardiovascular abnormalities, it is believed that other features of the condition are due to involvement of genes flanking elastin. A number of genes including LIM-kinase 1 (LIMK1) replication factor C subunit 2 (RFC2), syntaxin 1A (STX1A), FZD3, GTF21, CPETR1, CPETR2, FKBP6, WSTF, WS-betaTRP, WS-bHLH, BCL7B, and transcripts including WBSCR1 and WBSCR4, are now known to lie within the deleted region.¹⁸⁻²⁷ With the exception of elastin, no definite role in the Williams phenotype has been shown for these other genes to date, and indeed for many genes haploinsufficiency is unlikely to have an effect.

LIM-kinase 1 encodes a novel protein kinase, which is expressed widely in development, and its unusual structural features suggest a possible role in cell signalling. Following a paper by Frangiskakis *et al* implicating LIMK in visuospatial construction cognition,⁷ this gene was widely reported in the American press to be the first "thinking" gene. However, subsequent evidence is conflicting and the jury is still out.²⁷

Neuroanatomical studies

Neuroanatomical studies indicate that the overall cortical volume in Williams syndrome is smaller than that of age matched normal controls. The neocerebellum, however, is normal or large and there is relative sparing of the frontal

Key messages

- Williams syndrome is caused by a microdeletion on chromosome 7 and the diagnosis can be confirmed by FISH studies
- Ongoing medical surveillance should include monitoring of blood pressure and renal function
- Williams syndrome is proving an interesting model for studying the molecular basis of cognition and behaviour

lobes and limbic system, which has been suggested as the reason for preservation of language functions and emotional responsivity.²⁸ In physiological testing, brains of people with Williams syndrome show lack of lateralisation for activity involved with grammatical stimuli and reversal of the usual right sided function in processing of facial imaging, both processes apparently spared in Williams syndrome suggesting that functions can be devolved in the brain despite abnormal developmental patterning.

Conclusion

Although Williams syndrome is a relatively rare condition, it is proving to be an interesting model for dissecting the underlying genetic basis for behavioural and cognitive phenotypes. Hopefully, continuing molecular genetic, neurobehavioural, and neurobiological studies in the next few years will prove fruitful in increasing our understanding of such mechanisms, which have implications far wider than the syndrome itself. Better understanding of the underlying genetic defect in Williams syndrome, particularly that involved in hypercalcaemia, might also have implications for treatment of those affected and for the non-Williams syndrome form of idiopathic infantile hypercalcaemia.

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Injury prevention

Worldwide, some 300 000 children die each year in road traffic crashes, a further 300 000 children drown, and some 100 000 die in fires.¹ Many millions of children are seriously injured and hundreds of thousands sustain permanent disabilities. The public health response to this human tragedy is pitiable and raises important questions for child health professionals. Why, for example, is the death of a child following abuse taken as clear evidence of the failure of our collective efforts to protect children, whereas a child pedestrian death represents only the failure of an individual child to stop, look, and listen when crossing the road? And why did medical research “declare war” on cancer and ignore injury, when as many children die from injury as from all forms of cancer combined?

Most of the road deaths, particularly those in the developing world, involve children as pedestrians.² In Britain, the pedestrian injury epidemic peaked in the 1930s with an average of nine deaths each day.³ Since then death rates have fallen, but not necessarily because our roads have become safer. On the contrary, the two most likely explanations for the decline in child pedestrian deaths are the massive reduction in walking that has accompanied increasing traffic volume,⁴ and the increased survival chances of seriously injured children from improvements in hospital care.⁵ There can be little doubt that in the struggle for the streets, the pedestrian lost, with tens of thousands of children killed in the process. But for most of the world the battles are just beginning. Like so many Western epidemics, the pedestrian injury epidemic is now being exported to the developing world. European and North American car markets are reaching saturation point and motor manufacturers are looking east. The road death epidemic in China is only just beginning, but already an estimated 29 000 children are killed on the roads each year,¹ and the epidemic will generate a mountain of disability. It is estimated that by 2020 road traffic accidents will be the third leading cause of disability adjusted life years (DALY) worldwide, and the second leading cause of DALYs in the demographically developing countries.⁶

An epidemic of this scale demands an appropriate and timely public health response. It is a matter of urgency that effective strategies are identified for the prevention of road traffic accidents, drowning, fire deaths, and other leading causes of injury, and for the treatment and rehabilitation of injured victims, particularly in low income countries. A logical first step would be to find out what we already know about the effectiveness of injury prevention and injury management by conducting systematic reviews of control-

led intervention studies, and of case-control and cohort studies where no intervention studies are available. The Cochrane Injuries Group, an international network that prepares, maintains, and promotes the accessibility of systematic reviews of the effectiveness of interventions in the prevention, treatment, and rehabilitation of injury has been established to facilitate this process.⁷ To date, findings from systematic reviews include the demonstration that random breath testing reduces road deaths,⁸ that pool fencing reduces the risk of drowning,⁹ and that albumin infusion for hypovolaemia following trauma is of no proved benefit and may even increase the risk of death.¹⁰

The effectiveness of some prevention strategies is not in doubt, but for many mechanisms of injury the value of preventive measures remain uncertain, and large scale randomised controlled trials are required to determine their effectiveness. For a problem as common as injury, even moderate intervention effects would be important. However, to detect reliably moderate effects, both moderate biases and moderate random errors must be avoided.¹¹ Injury prevention trials must therefore be large enough to avoid moderate random errors and should be designed in such a way that moderate biases are avoided. Some injury prevention interventions cannot be implemented separately for each individual and individual level randomised controlled trials will not be possible. Evaluation of these strategies requires community intervention trials, and recent developments in the methodology of cluster randomised controlled trials will facilitate these.¹² Probably the main obstacles to the conduct of such studies are political rather than methodological: first the importance of random allocation in the unbiased assessment of effectiveness is not widely appreciated in areas such as transport, housing, and education; second, injury research is grossly underfunded compared with other health problems.¹³

The identification of effective injury prevention interventions is necessary but not sufficient to prevent childhood injuries. Many injury prevention strategies require structural change and will encounter strong opposition from vested interests. The strategy for overcoming structural barriers to child health is advocacy. Advocacy is structural therapeutics, which, to date British paediatricians have shown a notable reluctance to prescribe.¹⁴ But there are encouraging signs that things are now changing, as evidenced by the support by the Royal College of Paediatrics and Child Health for the Road Traffic Reduction (UK Targets) Bill.¹⁵ Striving to make a better world for