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Williams-Beuren syndrome in the Hong Kong Chinese population: retrospective study

香港華裔人口中的Williams-Beuren綜合症：回顧研究

Objective. To estimate the incidence and document the clinical characteristics of Williams-Beuren syndrome in the Hong Kong Chinese population.

Design. Cytogenetic analysis and retrospective study.

Setting. Clinical Genetic Service, Department of Health, Hong Kong.

Patients. Forty-one Chinese patients with Williams-Beuren syndrome.

Main outcome measures. From 1 January 1995 to 30 June 2002, fluorescence in situ hybridisation was used to confirm diagnoses in 41 cases of Williams-Beuren syndrome by detecting chromosome 7q microdeletion. Case records were reviewed, the incidence of the condition in the local population was estimated, and the main clinical characteristics were determined.

Results. The minimal incidence of Williams-Beuren syndrome in this locality was estimated to be approximately 1 per 23 500 live births. Common dysmorphic facial features included periorbital fullness (83%), full lips (80%), a long philtrum (51%), a flat nasal bridge (41%), and abnormal teeth (37%). No patients had a stellate iris. The majority (82%) had at least one documented cardiac anomaly; among these patients, peripheral pulmonary stenosis was diagnosed in 61% and supravalvular aortic stenosis in 45%. Nearly all (93%) of the study group exhibited developmental delay.

Conclusion. As in the West, patients with Williams-Beuren syndrome in the Hong Kong Chinese population display craniofacial dysmorphism, cardiovascular anomalies, and mental deficiency. Supravalvular aortic stenosis—the cardiac defect most commonly associated with Williams-Beuren syndrome in western countries—is less common than peripheral pulmonary stenosis in this region. Studies involving periodic cardiovascular evaluation are needed to confirm if this difference is significant.

Key words:

Abnormalities, multiple;
Genetic disease, inborn;
Williams syndrome

關鍵詞：

異常，多方面；
遺傳病，先天的；
Williams 綜合症

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目的：評估Williams-Beuren綜合症在香港華裔人口中的發病率，並記錄香港華人患者的臨床特徵。

設計：細胞遺傳學分析及回顧研究。

安排：香港衛生署醫學遺傳科。

患者：41名Williams-Beuren綜合症華人患者。

主要結果測量：從1995年1月1日至2002年6月30日期間，以螢光原位雜交檢測技術偵測41名病者的染色體7q有輕微缺失，從而確定他們患有Williams-Beuren綜合症。通過檢視患者的病歷，從而評估病症在香港的發病率，並確定其主要的臨床特徵。

結果：香港的Williams-Beuren綜合症發病率，估計為每23 500個出生並存活嬰兒中至少一宗。常見的面部畸形特徵包括眼皮腫脹(83%)、唇厚(80%)、人中長(51%)、鼻樑扁平(41%)，以及牙齒異常(37%)。病人當中沒有發現星狀虹膜，大部分(82%)病者的病歷顯示至少一項心臟異常紀錄。這些病者中，61%患有周邊肺動脈狹窄，45%則有主動脈瓣上狹窄。幾乎所有病者(93%)均出現發展遲緩的情況。

結論：和西方國家的患者一樣，香港華裔Williams-Beuren綜合症患者出現顛面畸形、心血管系統異常，以及智力遲緩。主動脈瓣上狹窄是最常見於西方國家Williams-Beuren綜合症患者的相關狀況，但此狀況在香港的Williams-Beuren綜合症患者中，不及周邊肺動脈狹窄普遍。至於此項差異是否顯著，有待包括定期心血管系統評估的進一步研究確定。

Introduction

Williams-Beuren syndrome (WBS) is a rare congenital neurodevelopmental disorder characterised by dysmorphic facies, cardiovascular disease, mental insufficiency, idiopathic hypercalcaemia, growth deficiency, characteristic personality, and peculiar cognitive profile. The syndrome was first described in 1961 by Williams et al,¹ who reported on a group of children with supravalvular aortic stenosis (SVAS), dysmorphic facies, and mild mental retardation. In 1964, Beuren et al² independently described the syndrome and identified its association with peripheral pulmonary stenosis (PPS), dental anomalies, and friendly personality of affected children.

The incidence of WBS is estimated to be about 1 in every 20 000 to 50 000 live births worldwide.^{3,4} Males and females are equally affected. Conventionally, diagnosis of WBS is made on the basis of clinical assessment. Most children with WBS have characteristic craniofacial features—namely, curly hair, broad forehead, periorbital fullness, medial eyebrow flare, stellate iris, flat nasal bridge, bulbous nasal tip, long philtrum, wide mouth, full cheeks and lips, and small and widely spaced primary teeth (Fig 1).⁵ These typical facial features tend to become more prominent as the child develops.

About 80% of patients with WBS have cardiovascular disease. Supravalvular aortic stenosis, the most common



Fig 1. A 9-month-old girl with characteristic craniofacial features of Williams-Beuren syndrome: curly hair, periorbital fullness, flat nasal bridge, long philtrum, and thick lower lip

heart lesion, is present in about 75% of patients. Other common cardiovascular problems in WBS include PPS, renal artery stenosis, hypertension, and arterial stenosis.⁶

Mental insufficiency is present in most patients with WBS. They typically have mild-to-moderate grade mental retardation, with an average full-scale intelligence quotient (IQ) of 50 to 60.⁶ Individuals with WBS tend to have relatively preserved language abilities but poor visual-spatial skills. Behavioural problems, such as hyperactivity, easy distractibility, overfriendliness, and unusual loquacity, are also common.⁷

Some infants with WBS have hypercalcaemia, which may lead to irritability, colic, vomiting, constipation, and muscle cramps. The prevalence and underlying cause of hypercalcaemia among these patients remain unknown, but the hypercalcaemia usually resolves spontaneously.^{6,7}

Mild prenatal growth deficiency and subnormal postnatal growth are consistently observed features of WBS. Most children with WBS have a slightly low birthweight. Growth disturbance with failure to thrive is a common problem among patients with WBS during infancy and childhood.⁷

In 1993, the deletion of the elastin (*ELN*) gene was implicated in the pathogenesis of WBS. The hemizygous submicroscopic deletion on the long arm of chromosome 7 (7q11.23) is now found in more than 90% of individuals with WBS.^{8,9} Detection of the deletion by fluorescence in situ hybridisation (FISH) is the most sensitive confirmatory test, although it has little prognostic value, because most patients—despite their variable clinical manifestations—have a common chromosomal deletion of an approximately 1.5 million bases. However, the importance of having a confirmed diagnosis is not to be understated; it facilitates genetic counselling, family screening, and the formulation of a long-term management plan for the patient.

Most published studies on WBS include only patients from western countries. In this study, we aimed to explore the clinical characteristics of WBS in the local Chinese population.

Methods

Patients

The Clinical Genetic Service of the Department of Health is a tertiary referral centre in Hong Kong that offers diagnostic, counselling, and laboratory services to individuals and families with genetic diseases. Patients were referred from other medical professionals all across the territory, with or without suspicion of a specific diagnosis. A detailed history was taken and a thorough physical examination was performed at the genetic counselling clinic. Blood was taken for genetic investigation if indicated. In 1995, our cytogenetic laboratory started using the FISH technique to detect microdeletion of

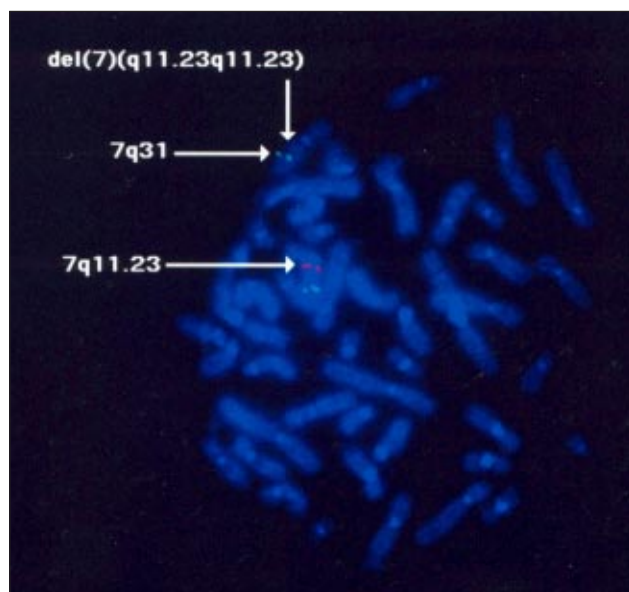


Fig 2. Photomicrograph showing microdeletion at chromosome 7

Fluorescence in situ hybridisation shows an orange signal specific for Williams-Beuren syndrome chromosome region at loci 7q11.23 and a green signal specific for control loci at 7q31

chromosome 7q11.23 for patients who, after clinical assessment by the clinical geneticist, were suspected of having WBS. These patients were then followed up regularly to monitor their long-term progress. In this study, the clinical data in the case records of all patients confirmed to have WBS from 1 January 1995 to 30 June 2002 were reviewed retrospectively.

Cytogenetic study

Peripheral blood was taken from all subjects with suspected WBS, and cytogenetic analyses were performed using standard methods: metaphase chromosomes were obtained from phytohaemagglutinin-stimulated whole blood cultures and chromosome spreads were processed for G-band staining using trypsin and Giemsa stain. In the FISH method, a locus-specific, fluorescently labelled DNA probe is used to detect submicroscopic chromosomal abnormalities. The hybridisation step consists of mixing heat-denatured probe with heat- and formamide-denatured chromosome spreads on a glass slide. This process allows annealing of the probe to the complementary target DNA. The fluorescence signals on the chromosome slide can then be visualised under the microscope.

Between 1995 and 1999, we used the Elastin Williams syndrome chromosome region probe (P5155-DG.5; Oncor, Inc., Gaithersburg [MD], US) for FISH detection; with D7S427 probe as a chromosome 7 control. After 1999, we used dual-colour Locus Specific Identifier Williams Syndrome Region probe (32-190041; Vysis, Inc., Downers Grove [IL], US) that hybridise to the *ELN* and *LIM* kinase 1 (*LIMK*) loci at 7q11.23, as well as to two control loci at 7q31: D7S486 and D7S522 (Fig 2).

Results

Up to 30 June 2002, 41 patients with clinical diagnoses of WBS, including 38 with sporadic WBS and three with the familial form, were confirmed by FISH to have WBS. Two patients were identified after family screening. Nineteen patients were male and 22 were female, giving a male to female ratio of 1:1.16. The mean age of presentation in all 39 index cases was 4.1 years (range, 1 month-17.1 years).

The 39 index cases were referred to the Clinical Genetic Service from different sources, including general paediatricians, paediatric cardiologists, developmental paediatricians, a paediatric neurologist, a paediatric endocrinologist, and a neonatologist. The problems that patients presented with in these cases were as follows: 16 (41%) had a heart murmur or congenital heart disease, 13 (33%) had developmental delay or mental retardation, three (8%) had dysmorphic features, three (8%) had heart problem and dysmorphism, two (5%) had heart lesion and developmental delay, one (3%) failed to thrive, and one (3%) had short stature.

Incidence

Among all 41 patients with WBS, 21 were born during the study period but only 17 of these were born in Hong Kong. According to the vital statistics published by the Department of Health of the Hong Kong Special Administrative Region, the total number of live births from 1995 to 2001 was 399 051. Hence, the minimal incidence of WBS in our locality is estimated to be 1 in 23 474 live births.

Chromosomal abnormalities

Three patients were found to have co-existing chromosomal abnormalities in addition to the chromosome 7q microdeletion—namely, 47,XXX, 46,XX,inv(2)(q31q35), inv(9)(p11q13), and 46,XX,inv(18)(p11.23q11.2).

Family screening

When an index case is identified, confirmation by FISH is offered to the patient's parents and, if indicated, to other siblings as well. In our study, 69 parents and siblings in 36 families had FISH confirmation performed. Family screening was not done in three families because they failed to attend the follow-up session.

We detected chromosome 7q microdeletion in two family members, both of whom were from one family: the proband's mother and younger brother (twin 2). The proband's other, younger brother (twin 1) had cardiovascular problems (atrial septal defect and PPS) and similar facial features as twin 2. However, twin 1 died of sagittal vein thrombosis with subdural and subarachnoid haemorrhage at the age of 2 years, before we could perform the confirmatory test for WBS.

Most cases of WBS are caused by de novo hemizygous microdeletion, and familial cases follow an autosomal

Table 1. Cardiovascular anomalies in Chinese patients with Williams-Beuren syndrome (with American Academy of Pediatrics [AAP] data⁶ for comparison)

| Cardiovascular anomalies | Patients, n=31 No. (%) | AAP data (%) |
|--|---------------------------|--------------|
| Peripheral pulmonary stenosis | 19 (61) | 50 |
| Supravalvular aortic stenosis | 14 (45) | 75 |
| Atrial septal defect | 6 (19) | NA* |
| Valvular pulmonary stenosis | 2 (6) | 25 |
| Coarctation of aorta | 2 (6) | NA |
| Ventricular septal defect | 1 (3) | 10 |
| Bicuspid aortic valve with aortic regurgitation | 1 (3) | NA |
| Small ascending aorta/aortic arch | 1 (3) | NA |
| Narrowing of descending aorta | 1 (3) | NA |
| Mitral valve prolapse with mild mitral regurgitation | 1 (3) | NA |
| Other arterial stenosis | 0 | 20 |
| Hypertension | 0 | 50 |

* NA not available

dominant pattern of inheritance. In our study, other family members were affected in only one (3%) of 36 families.

Facial dysmorphism

When we assessed facial features of the 41 patients from records (before the confirmatory genetic testing), we found that 34 (83%) had periorbital fullness, 33 (80%) had full lips, 21 (51%) had a long philtrum, 17 (41%) had a flat nasal bridge, and 15 (37%) had either widely spaced or small irregular teeth. Other features of the disease were uncommon, and none of the patients had a stellate iris.

Cardiovascular disease

Among the 41 patients, most (n=38) had cardiological evaluations performed; seven of these patients had normal echocardiographic findings. Two patients with normal cardiovascular examination results received no formal echocardiographic evaluation during the study period, and one patient with heart murmur did not attend follow-up.

Thirty-one (82%) of 38 patients with WBS who had undergone echocardiographic assessment had at least one documented cardiovascular anomaly. Among these anomalies, the two most common were PPS (19/31; 61%) and SVAS (14/31; 45%) (Table 1). None of the patients in this series died of heart failure, and only one patient with both PPS and SVAS required surgical intervention.

Growth deficiency

The mean birthweight of the 39 index patients, whose gestational age ranged from 33 to 44 weeks, was 2.58 kg (standard deviation, 0.36 kg; range, 1.81-3.70 kg). Of the 41 patients confirmed to have WBS, 19 (46%) had a height at the third centile or lower, 33 (80%) had a height at the 25th centile or lower, and 37 (90%) had a height at the 50th centile or lower. As for bodyweight, 19 (46%) patients were at the third centile or lower, 25 (61%) were at the 25th centile or lower, and 30 (73%) were at the 50th centile or lower.

Mental insufficiency

Of the 41 patients with WBS, 38 (93%) were known to have delayed mental development. The degree of mental

Table 2. Other medical problems in Chinese patients with Williams-Beuren syndrome (with American Academy of Pediatrics [AAP] data⁶ for comparison)

| Condition | Patients, n=41 No. (%) | AAP data (%) |
|--------------------------------------|---------------------------|--------------|
| Inguinal hernia | 7 (17) | 40 |
| Hypothyroidism | 5 (12) | 2 |
| Structural genitourinary abnormality | 3 (7) | 20 |
| Multicystic kidney | 1 (2) | - |
| Duplex kidney | 1 (2) | - |
| Hypospadias | 1 (2) | - |
| Congenital ptosis | 1 (2) | NA* |
| Hearing deficit | 1 (2) | NA |
| Epilepsy | 1 (2) | NA |

* NA not available

insufficiency that each patient displayed, however, was not documented in the case records.

Idiopathic hypercalcaemia

Only 17 of the 41 patients had their blood calcium level documented in the case records (range, 2.13-3.09 mmol/L). Three patients had calcium levels higher than the normal range (2.2-2.6 mmol/L), but one of these had a normal level after rechecking. Initial calcium levels of the other two patients were slightly higher than the normal range (2.66 mmol/L and 2.67 mmol/L) and blood tests have not yet been repeated. No patient required medical treatment for hypercalcaemia.

Other medical problems

In this study, the most common other type of medical problem was inguinal hernia, detected in seven (17%) of the 41 patients, followed by hypothyroidism (5/41; 12%). Other problems included structural genitourinary abnormalities, congenital ptosis, hearing deficit, and epilepsy (Table 2). However, because some investigations, such as screening of thyroid function and renal ultrasonography, were not performed for all patients in our study group, our data may not reflect the true frequency of these medical problems in local Chinese patients who have WBS.

Discussion

Williams-Beuren syndrome, characterised by distinctive

facies, cardiovascular anomalies, mental retardation, and unique personality, is a rare genetic condition caused by hemizygous microdeletion on the long arm of chromosome 7 (7q11.23). The deletion is thought to be caused by unequal meiotic recombination between the chromosome 7 homologues, mediated by highly homologous low-copy repeated sequences.¹⁰ Osborne et al¹¹ found that the presence of a 1.5-megabase inversion at the WBS region might also be a predisposing factor.

In 1993, Ewart et al⁸ identified the cause for WBS to be hemizygosity at the *ELN* locus resulting from a microdeletion on chromosome 7. Further analysis of the region around the *ELN* locus in patients with WBS demonstrates that most of them have a common deletion spanning approximately 1.5 megabases that include at least 17 genes at 7q11.23.¹² The deleted *ELN* gene in WBS encodes the structural protein elastin, which is an important component of elastic fibres in the connective tissues of various organs (eg larger blood vessels and vocal cord). This deficiency explains some of the features in WBS—namely, SVAS, hypertension, and hoarse voice.^{6,10}

Some other clinical features of WBS, such as mental retardation, hypercalcaemia, and unique personality traits, are not attributable by elastin haplo-insufficiency.⁶ Although some other genes, such as the *LIMK1* gene, within the WBS critical region have been studied, the relationship with the WBS cognitive phenotype remains unclear at present.¹³

In this study, 41 cases of WBS, confirmed by FISH to have microdeletion on chromosome 7, were reviewed. A study of patients' parents showed that only a small proportion of cases were familial. This finding agrees with those of overseas studies. The minimal incidence of WBS is estimated to be approximately 1 per 23 500 live births in our locality, and this figure is comparable to the commonly quoted incidence in overseas studies. The actual incidence could be higher than our estimated figure, because some patients with WBS may not have been referred to our centre during the study period, especially if they did not present with the typical features (eg congenital heart disease and developmental delay).

Of the 41 confirmed cases with WBS, three patients had co-existing chromosomal abnormalities; one had an XYY genotype. Most XYY males are phenotypically normal, although they may have an increased risk of language difficulties and behavioural problems. Because XYY is a relatively common chromosomal abnormality, occurring in about 1 in 1000 males, it is probably coincidental that the abnormality occurred in one of the patients in our series. In addition, there were no reports that suggested predisposition to chromosome microdeletion in the patients with aneuploidy. However, how the XYY genotype may influence the phenotype of WBS, particularly regarding neurodevelopment, is not yet known.

For the patient with paracentric inversion of chromosome 2 and pericentric inversion of chromosome 9 [46,XX,inv(2)(q31q35),inv(9)(p11q13)], the inv(2)(q31q35) was also found in the phenotypically normal father and paternal grandmother, whereas the inv(9)(p11q13) was found to be inherited from the mother. For the patient with pericentric inversion of chromosome 18 [46,XX,inv(18)(p11.23q11.2)], the parents were phenotypically normal. The mother's karyotype was normal, but the father was not available for karyotyping. Hence, it remains possible that this abnormality is a de novo inversion, in which case there is approximately 15% risk of phenotypic abnormality. However, the phenotypic effect associated with the inversion, if there is any, is difficult to predict, so the ultimate influence on the WBS phenotype in this patient is unknown.

The pericentric inversion of chromosome 9 is a known normal variant, but the paracentric inversion of chromosome 2 and the pericentric inversion of chromosome 18 are not. Pericentric inversions other than the normal variants such as inv(9)(p11q13) have a prevalence of 0.12% to 0.70%, whereas paracentric inversions have a prevalence of 0.10% to 0.50% in general.¹⁴ It seems that the study group had an unexpectedly high frequency of chromosomal inversions. None of these inversions were on chromosome 7, suggesting that they are unlikely to be directly involved in the formation of the microdeletion. Nevertheless, the high frequency of inversion may indicate a general tendency of genomic rearrangement in these individuals, which in turn leads to the formation of microdeletion.

Dysmorphic facies, cardiovascular anomalies, and mental insufficiency are consistent findings in WBS, and all patients in our study group had at least one of these classic features. More than 50% of patients had periorbital puffiness, full lips, and long philtrum. None of them had stellate iris, which is more frequently seen in green- and blue-eyed children.

Cardiovascular anomalies are seen in about 80% of patients with WBS.⁶ Supravalvular aortic stenosis, the most common cardiac lesion in WBS in the West, according to the literature, is a progressive condition that may require surgical repair. In contrast, PPS often presents at birth and tends to improve over time. The American Academy of Pediatrics (AAP) recommends periodic cardiovascular evaluations even if a baseline examination yields normal results. Our data showed that cardiovascular abnormalities were present in 82% of patients with WBS and a wide spectrum of cardiac abnormalities was seen, with PPS being the most common lesion, followed by SVAS. The discrepancy between our study and the literature could be due to the relatively small sample size in our study. It is also possible that some patients develop SVAS at an older age and a higher proportion of SVAS cases could be identified with a longer follow-up period. Alternatively, the discrepancy may reflect a genuine ethnic difference in genetic background that plays a role in modifying the phenotypic manifestation of the microdeletion.

Hypertension is more common in children and adults with WBS than in age-matched members of the general population, and it occurs in approximately one third of patients with WBS.⁵ Risk for hypertension may increase with age, and periodic screening of hypertension is essential in patients who have WBS.^{5,6} In a retrospective study of cardiovascular manifestations in WBS in Finland, 23 (55%) of 42 patients older than 15 years had hypertension and 14 of them required antihypertensive treatment.¹⁵ Because only a few of our patients had their blood pressure measured and documented in case records, periodic blood pressure measurement during the clinic visit may allow early recognition and appropriate treatment of this condition in our patients.

Growth deficiency is also a common feature seen in our study group as nearly half (46%) of our patients had their heights and body weights at the third centile or lower. The majority (93%, n=38) of patients in this study had documented developmental delay. Not all of the patients had formal psychological and IQ assessments; hence, their exact extent of mental retardation and behavioural profiles cannot be reviewed. Impaired visual-spatial ability is a consistent cognitive phenotype seen in WBS, and some performance tests, such as the test of visual motor integration, the Benton judgement of line orientation and the block design subtests of the Wechsler intelligence scales, could be used to assess this ability.¹⁰ Given that the peculiar cognitive profile is an important feature of WBS, further study concerning mentality and behaviour patterns is worthwhile.

The management of children with WBS requires an understanding of the natural course of the disorder, awareness of potential clinical complications, and periodic review at different ages. A policy statement released by the AAP in 2001—'Health care supervision for children with Williams syndrome'—included a set of guidelines to assist the paediatrician to care for children with WBS from early infancy to adolescence. The guidelines recommend baseline and ongoing cardiological, ophthalmological, auditory, and growth and developmental evaluations, as well as periodic blood pressure measurement, urinalysis, calcium level determination, renal and thyroid function testing, and

ultrasonography of the bladder and kidney at appropriate ages.⁶ The establishment of similar guidelines for Chinese patients with WBS is essential, and periodic assessments may improve the medical care for patients who have WBS and allow better understanding of physical and behavioural phenotypes of this disorder.

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