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Educational Article

Williams–Beuren syndrome: a complete guide for oral healthcare

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Abstract – Introduction: Williams–Beuren syndrome is a rare, congenital, multisystem disorder, resulting from genetic alterations on chromosome 7q11.23. Characteristic features of WBS are the developmental, physical and mental abnormalities associated with it. Typical facial features and a spectrum of tooth disorders are associated with this condition. Cardiac and renal involvement may be so severe that sudden death during oral healthcare procedures is a possibility. Photophobia and hyperacusis further make dental treatment a challenge in these patients. **Corpus**: Routine dental treatment in the dental office pose a significant risk, depending upon the mental and physical compromise of the patient, thereby making hospital admission a safer approach. A multispeciality approach is necessary to provide effective and safe oral healthcare to such patients. This article provides undergraduates, residents, general dental practitioners, and specialists involved in oral healthcare with a comprehensive overview of the condition with emphasis on its genetic basis, pathology, clinical features, diagnosis, and management of general and oral health. **Conclusion**: Adequate knowledge regarding the various aspects of Williams–Beuren syndrome allows the oral health care student or specialist to plan and manage oral procedures safely and effectively. Specialist referral and multidisciplinary care may be considered when appropriate.

Introduction

Williams–Beuren syndrome [WBS] is a rare, congenital, panethnic, multisystem disorder, that is a result of genetic alterations on chromosome 7q11.23 [1]. The disorder is alternatively known as Williams syndrome, Elfin facies syndrome, chromosome 7q11.23 deletion syndrome [2]. Characteristic features of WBS are the developmental, physical and mental abnormalities associated with it.

WBS was first described in 1961 Dr John Williams, a cardiologist, who reported four children with similar facies, supravalvar aortic stenosis, cognitive impairment, learning difficulties and love for music [3]. Strabismus, pulmonary artery stenosis and tooth abnormalities were added as characteristics of the syndrome in 1962 by Dr Beuren [3]. Online Mendelian Inheritance in Man database has assigned a number #194050 to WBS.

The inheritance pattern of WBS is recognized to be of autosomal dominant type [1]. WBS mainly occurs sporadically, with incidence ranging from 1:20 000 to 1:50 000 [3]. There is no gender dominance in inheritance and the disorder is reported in all ethnicities around the world [3].

The learning objectives of this article include the development of the ability of the oral healthcare student or professional to identify a patient with WBS, diagnose the case, and plan a comprehensive oral health care regimen for the patient. Multidisciplinary consultations and referrals can then be made depending upon each case.

Aetiopathology

The first report on the aetiology of WBS proposed Vitamin D teratogenicity as the likely cause. This presumption was made on the basis of experiments on rabbit foetuses which showed supravalvar aortic stenosis and craniofacial abnormalities upon being exposed to high doses of vitamin D [1]. However, two findings subsequently proved that WBS was genetic, not teratogenic. These two findings were (1) parent to child transmission and (2) discovery of phenotypically overlapping autosomal dominant familial supravalvar aortic stenosis syndrome (OMIM number, 185500) [1].

It is now accepted that WBS is a micro-deletion disorder, caused by deletion/loss of a segment of DNA referred to as the WBS critical interval. This interval on chromosome 7q11.23 extends from 1.5 to 1.8 million base pairs, containing 26–28 genes [4]. Therefore, WBS patients carry only a single copy of these 26–28 genes, in contrast to unaffected individuals who

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Table I. Clinical features of Williams–Beuren syndrome.

Growth disturbances	Intrauterine growth disturbances, short stature, abnormal weight gain
Cardiac	Supravalvar aortic stenosis [SVAS, 70% of patients], aortic arch or descending aorta hypoplasia, aortic stenosis, bicuspid aortic valve, mitral valve prolapse [15% of patients], mitral regurgitation, coronary artery stenosis, pulmonary artery stenosis [PAS, 45% of patients], atrial septal defect [ASD], ventricular septal defect [VSD], Tetralogy of Fallot
Vascular	Peripheral pulmonary artery stenosis, systemic hypertension
Respiratory	Pectus excavatum, obstructive sleep apnoea
Auditory/ENT	Sound hypersensitivity, recurrent ear infections, sensorineural hearing loss
Abdominal	Inguinal/epigastric hernia
Gastrointestinal	Chronic constipation, diverticulosis, colic, feeding difficulties, gastro esophageal reflux, intolerance to ingestion of textured food
Renal	Small kidneys, single kidney, pelvic kidney, nephrocalcinosis, renal insufficiency and renal artery stenosis
Urinary	Bladder diverticula, urethral stenosis, recurrent urinary tract infections, voiding frequency/urgency, enuresis and delayed toilet training
Endocrine	Early puberty, glucose intolerance or diabetes mellitus subclinical hypothyroidism, hypercalcemia
Neurologic	Hypotonia (infants), hypertonia (children/adults), poor balance, tremors, Chiari Type I malformation, mental retardation, relative sparing of language, poor visual-motor integration, poor visual-spatial construction
Behavioral/Psychiatric	Attention deficit disorder, friendly personality, strong affinity to music, anxiety, phobias, obsessive-compulsive traits
Ophthalmologic	Strabismus, hyperopia/myopia, poor depth perception, lacrimal stenosis, sllate pattern of iris
Skin/Integument	Soft skin (baby soft), premature hair greying, splaying of skin during wound healing, hypoplastic nails
Musculoskeletal	Joint contractures/laxity, osteopenia, osteoporosis, kyphoscoliosis, joint limitation in limbs, hallux valgus deformity, poor balance, poor coordination
Vocal	Harsh, brassy or hoarse voice

carry two copies of each of these genes [4]. Deletion of the WBS critical interval brings about the spectrum of features that characterise WBS. The size of the deletion is similar across all WBS patients, although considerable variability in the extent of physical and mental abnormalities. This aspect of WBS is derived from the fact that 'duplicons' or repetitive DNA segments, crowd around the WBS interval, thereby exposing the chromosome 7 pair to mispairing during meiosis [4]. This suggests that WBS arises from the nature of the genetic material on chromosome 7q11.23 and is not influenced by extrinsic factors such as parental influence or environmental exposures.

The deletion of a copy of the elastin gene [ELN] is thought to be the primary factor responsible for the development of cardiovascular features and certain musculoskeletal features of WBS [4]. The autosomal dominant inheritance pattern implies that affected individuals may have a 50% chance of producing WBS children. Healthy parents with a WBS child have a low risk of recurrence. However, somatic cell mosaicism remains a relative possibility [5].

Clinical features

WBS includes a myriad of physical, developmental and neuro cognitive disorders. These features are listed in (Tab. I) [6–9]. If supravalvar aortic stenosis [SVAS, moderate to severe form] is left untreated, it may progress to left ventricular hypertrophy or heart failure [7]. SVAS is also associated with risk of sudden death in WBS patients, a likely outcome of compromised coronary perfusion [7]. Sudden death can also occur under general anaesthesia, as a result of decreased coronary artery perfusion pressure [7]. In contrast, pulmonary artery stenosis [PAS] often regresses and resolves over time in WBS.

Pectus excavatum denotes a sunken or caved-in chest, usually a result of deformity of the rib cage and sternum, leading to a structural alteration of the anterior thoracic wall [6]. Chiari malformation type I refers to a condition in which a small or deformed skull causes the brain (cerebellum) to be displaced into the upper spinal canal [9]. Kyphoscoliosis denotes a spinal deformity in which the spine is abnormally curved, both in the coronal and saggital planes [9]. A hallus valgus deformity results in painful disability and denotes the malpositioning of the first metatarsophalangeal joint as a result of lateral deviation of the great toe with a medial deviation of the first metatarsal bone [9]. Paralysis of the vocal chords may bring about a rough or coarse voice in WBS individuals [6].

The orofacial features characteristic of WBS are listed in (Tab. II) [5,6,10–13] and illustrated in (Fig. 1). Mass and

Table II. Orofacial features of Williams–Beuren syndrome.

INTR oral	Extra oral
Angle Class II and III Malocclusion	Prominent thyroid cartilage
Open/cross bites	Full lips
Mild micrognathia	Wide mouth
Anterior crossbite	Widened mandibular angle
Osteosclerotic changes in the premolar- molar	Small chin
Lamina dura	Periorbital fullness (puffy eyes)
Folded and thickened buccal mucosa	Long face
Prominent accessory labial frenula	Medial eyebrow flare
Enamel hypoplasia	Flat midface
Enamel hypomineralization	Epicanthal folds
Microdontia	Long philtrum
Small tooth roots	Depressed nasal bridge
Delayed mineralization	Broad nasal tip
Invaginated incisors	Anteverted nostrils
Tongue thrusting,	Curly blond hair
Excessive interdental spacing	
Tapered or screwdriver shaped incisors	
Tooth agenesis	
Higher incidence of gingival and periodontitis	
Cleft palate (rare)	

Belostoky [10], in 1993, described four skeletal features as characteristic of the facial features of children with WBS: shortened anterior skull base, steep mandibular plane angle, disproportionate upper-to-lower anterior facial height and posterior-to-anterior facial height, although overall facial height is unaffected, and a deficient albeit non-retrognathic chin [11]. The dysmorphic facial features in WBS syndrome are typically known as "elfin facies" [12]. Maritsi *et al.* reported a case of benign paroxysmal torticollis (BPT) in a 14 month old with WBS [14]. Cingano *et al.* observed that in younger patients, poor oral hygiene measures brought about by a combination of factors such as lack of co-operation from patients, malocclusion and tooth agenesis resulted in a higher prevalence of gingival and periodontal diseases [15]. Furthermore, the authors stressed on the absence of the gene located on chromosome 7 in these patients which regulates the formation of elastin. Absence or significant alteration of elastin in the connective tissue of the gingiva and periodontal ligament predisposes these tissues to damage from plaque microbes [15].

WBS is not usually associated with malignancy. However, two types of malignant tumours have been reported in WBS patients, namely lymphomas (2 cases of Burkitt lymphoma,one case of non-Hodgkin lymphoma and one of T cell lymphoblastic lymphoma) and gliomas (one case of astrocytoglioma and one case of anaplastic oligodendroglioma) [16]. WBS patients must therefore be investigated for presence of such tumours, especially when neurological symptoms fall outside those commonly noted with the disorder.

Diagnosis

According to the American Academy of Pediatrics (APP) [Committee on Genetics, 2001], the clinical diagnostic criteria for WBS is based on 7 groups of findings, each with specific scoring [17]. These findings are growth disturbances (1 point), behavior and development (1 point), dysmorphic facial features (3 points), echocardiographic disturbances evident of SVAS or peripheral pulmonary artery stenosis (5 points) and other cardiovascular disorders (1 point), connective tissue disorders (2 points), and serum calcium assessment (2 points). If the total score is <3, then clinical diagnosis of WBS is unlikely and if ≥ 3, further investigations for WBS with genetic testing are recommended.

However, clinical presentation of WBS can be varied, courtesy of the atypical copy number variations (CNVs) associated with the chromosome region. In some instances, Noonan syndrome and Turner syndrome present with symptoms that may be identical to those of WBS, thus creating a diagnostic dilemma [18].

Genetic testing methods involve determination of the copy number of sequences on chromosome 7 and may include targeted deletion analysis by fluorescence in situ hybridization (FISH) technique [19]. Although the American College of Medical Genetics and Genomics (ACMG) recommends FISH as the primary diagnostic test for WBS, it is not ideal for the study of copy number variations (CNVs) [20]. Recently, two techniques namely Chromosomal microarray analysis (CMA) and Multiplex ligation dependent probe amplification (MLPA)

Fig. 1. Facial and dental features of WBS. (A and B) Skeletal class II malocclusion, mandibular retrognathism, dental biprotrusion, thick lips. (C) deep bite, overjet, screwdriver shaped incisors and diastema. (D and E) thick lips, and small chin. (F) cross-bite, dental biprotrusion, and diastemas. (G and H) front and lateral pictures showing wide mouth, midface flattening.

have been successfully applied to detect the CNVs in the 7q11.23 regions [21].

General health management

The American Academy of Pediatrics Committee on Genetics, has laid down specific criteria for the healthcare supervision of children with confirmed WBS [22]. These guidelines are age-specific and assist the pediatrician in providing adequate care and guidance to the child through his/her developmental years through to adulthood. Table III presents the guidelines [22].

Special considerations for the WBS child must include: avoiding multivitamin preparations owing to possible untoward effects of vitamin D on serum calcium [22], minimizing endogenous production of vitamin D by the appropriate use of sunscreen lotions, periodic cardiovascular evaluations notwithstanding normal baseline findings, hypertension screening periodically, and establishment of a medical home with active participation of caregivers as partners in continual healthcare management [22]. When hypercalcemia is observed, a pediatric dietician/nutritionist must be consulted to implement and monitor dietary calcium restriction. A pediatric urologist referral should be considered. In case hypercalciuria is observed, repeated urine calcium-creatinine ratio (morning and afternoon) monitoring must be undertaken. In case of continual elevation, serum calcium is rechecked and renal ultrasonography is ordered for nephrocalcinosis [22].

Oral healthcare management

The cardiovascular disorders in WBS may be serious enough to place the patient's life at risk when dental treatment is rendered, either under local or general anaesthesia [18]. It is therefore imperative that the oral health care provider consults a pediatric cardiologist for possible antibiotic prophylaxis and other strategies to minimize the inherent risks (Table IV). Congenital heart defects account for 53–80% of individuals with WBS [5]. Antibiotic prophylaxis regime in such patients is 2 g or 50 mg/kg of amoxycillin orally, given 30 minutes to 1 hour prior to invasive procedures, according to the guidelines laid down by the American Heart Association and American

Table III. Guidelines for healthcare supervision of children through adulthood with WBS.

From birth to 1 year (infancy)
Examination: Examine clinical features, confirm diagnosis with FISH analysis, routine health checks with baseline evaluation, growth and developmental evaluations using WBS growth charts, baseline cardiac check by a cardiologist with pediatric expertise and experience, analyze feeding difficulties such as gastroesophageal reflux, refusal, disordered suck or swallow, vomiting or symptoms of colic, ophthalmologic check for strabismus, amblyopia or refractive errors, review for inguinal hernia, objective hearing assessment between 6 and 12 months as recurrent otitis media is usually present, blood pressure measurement in both arms annually with careful evaluation of femoral pulses, review of symptoms of constipation and its manage it, pediatric anesthesia consultation in case of surgical intervention is required.
Investigations: FISH to confirm clinical diagnosis, serum creatinine level, urinalysis, serum calcium, spot urine test for calcium-creatinine ratio, thyroid screening for newborns, examination of the urinary bladder and kidneys with ultrsonography (USG).
Anticipatory Guidance: Organize emotional support for the family from family, friends, clergy, orpublic support groups. Keep a check on increased risk for otitis media, recognize feeding difficulty in transition to textured foods, refer the infant to early childhood intervention program
1–5 years (early childhood)
Examination: Annual health check with specific auscultation of chest and abdomen for murmurs or bruits, growth and developmental evaluations using WBS growth charts, annual cardiac check from 1 to 5 years, keep watch for feeding problems such as rectal prolapse and manage constipation with stool softeners when needed, annual hearing and vision check (objective check before 3 years), examination of joints, muscle tone, spasticity, and hyperactive reflexes, blood pressure measurement in both arms annually with careful evaluation of femoral pulses, pediatric anesthesia consultation in case of surgical intervention is required, multidisciplinary approach to assess child development and initiate treatment through early intervention programs (0–3 years) or school based initiatives ($>$3 years).
Investigations: Annual urinalysis, total serum calcium assessment if it was raised at baseline or if symptoms arise, otherwise measure every 2–3 years. Measure urinary calcium-creatinine ratio every 2 years, thyroid function and serum creatinine every 4 years.
Anticipatory guidance: Organize emotional support for the family from family, friends, clergy, orpublic support groups. Keep a check on increased risk for otitis media, assess feeding difficulty, initiate therapy as required (physical, speech, language, occupational and sensory integration). Assess for constipation, unexplained fever must be investigated for urinary tract infection. Dialogue with family regarding developmental status of child, admission to early intervention programs and preschool programs.
5–12 years (late childhood)
Examination: Annual health check, growth and developmental evaluations using WBS growth charts, annual blood pressure measurement in both arms with careful evaluation of femoral pulses, cardiac evaluation as implied by previous clinical evaluations. When previous evaluations are negative, repeated cardiovascular assessment for arterial stenoses, hypertension must be undertaken at puberty. Ophthalmologic assessment (strabismus and hyperopia), and orthopaedic assessment for joint mobility limitation, spine problems like kyphosis, lordosis, scoliosis, and muscle spasticity. Annual vision and hearing check, pediatric anesthesia consultation in case of surgical intervention is required. Assess child'sschool readiness and devise an individual educational Plan at 5 years. Assess child developmental and psychoeducational status, assess for attention-deficit hyperactivity disorder/anxiety problems formally with a discussion on management.
Investigations: Annual urinalysis. Measure serum calcium if raised at baseline or symptoms appear, otherwise evaluate e level every 4 years. Thyroid evaluation every 4 years, urinary calcium-creatinine ratio every 2 years, and serum creatinine level every 2–4 years.
Anticipatory guidance: Assess child's school readiness, initiate therapy as required (physical, speech, language occupational and sensory integration). Vocational planning (long term), discuss issues such as sexuality, adolescence and puberty. Attention to diet and exercise since obesity usually affects late childhood. Consider management of anxiety with methods such as counseling, relaxation sessions, and medications. Discuss estate planning for parents of a child with special needs.
13–18 years (adolescence)
Examination: Annual health check, blood pressure assessment in both arms, growth and developmental evaluations using WBS growth charts, cardiac assessment as implied by previous clinical evaluations, pediatric anesthesia consultation in case of surgical intervention is required, ophthalmology consultation for hyperopia, orthopaedic assessment for problems such as joint mobility limitation, kyphosis, lordosis, scoliosis and muscle spasticity. Annual assessment for hearing and vision. Evaluation of developmental and psychoeducational status, school placement and resource enhancement, vocational training, social skills education targeting peer interaction. Assess for gastrointestinal abnormalities such as diverticulitis/ diverticulosis, cholelithiasis, and chronic constipation in cases with abdominal pain symptoms. Watch for evidence of generalized anxiety disorder.

Table III. (continued).

From birth to 1 year (infancy)
Investigations: Annual urinalysis, thyroid function assessment every 4 years, serum calcium measurement only if symptoms appear, otherwise every 4 years. Urine calcium-creatinine ratio every 2 years, ultrasonography of urinary bladder and kidneys at puberty and every 5 years thereafter, serum creatinine level every 2–4 years.
Anticipatory guidance: School placement, continue therapy as required (physical, speech, language occupational and sensory integration), discuss diagnosis with the adolescent and their support groups. Dialogue on sexuality and reproductive matters, support career counseling, reinforce independence, gradually transit to adult care (specifically for cardiac issues). Reinforce daily exercise regime to maintain range of motion, and suggest seeking immediate medical consultation for urinary tract or gastrointestinal issues. Address mental health issues early and seek professional assistance in management.

Note: The same guidelines mentioned for adolescents must be followed for adults with WBS.

Table IV. Risk factors for oral healthcare and specific treatement modifications required.

Risk factors	Treatment modifications
Cardiac defects	Antibiotic prophylaxis
Cardiac great vessel constriction, mental retardation	Conscious sedation, general anesthesia
High caries susceptibility	Dietary counselling, oral hygiene maintenance, topical fluoride applications, pit and fissure sealants, regular oral prophylaxis
Anxiety/uncooperative behaviour	Behaviour modification, conscious sedation
Wound dehiscence	Avoid mucoperiosteal flaps
Cardiac compromise	Mild cases treat in dental office without adrenaline use
Renal compromise	Avoid nephrotoxic drugs, NSAIDs and Aspirin Treat on the day following renal dialysis
Bleeding tendency	Bleeding and coagulation tests, local hemostatic measures, establish INR$\leq$2 before invasive procedures

College of Cardiology [23]. For those unable to take oral medication, ampicillin 2 g or 50 mg/kg orcefazolin/ceftriaxone 1 g or 50 mg/kg is administered IM/IV. Patients allergic to penicillins or ampicillin can be administred oral cephalexin 2 g or 50 mg/kg, clindamycin 600 mg or 20 mg/kg, azithromycin/clarithromycin 500 mg or 15 mg/kg. If patient is allergic to penicillins or ampicillin and unable to take oral medication, cefazolin/ceftriaxone 1 g or 50 mg/kg IM/IV or clindamycin 600 mg or 20 mg/kg IM/IV can be administered [24].

The great vessels of the heart constrict before the age of 5 years in WBS childrenand cardiac disease severity worsens with progressive age [5]. Therefore, before any dental intervention, cardiac status must be reviewed. Intravenous catheterization under general anesthesia has lead to myocardial infraction or cardiac arrest in infants [25]. Furthermore, significant morbidity and early (sudden) death in children in majority of cases is attributed to cardiac abnormalities such as arterial narrowing (stenosis), hypoplasia or coarctation [5].

Considering the cardiac risk factors, the fact that dental treatment may incite anxiety in WBS patients [5], mental retardation and tendency towards uncooperative behavior in the dental office, it will be prudent to think that dental treatment may preferably be provided under conscious sedation or general anesthesia in a hospital setting. However, there is no contraindication to routine dental treatment in the dental office, under local anesthesia, in cooperative patients with mild cardiac/systemic abnormalities. Collins *et al*. proposed a risk stratification system for anesthetic administration in WBS patients [26]. Table V presents this stratification system. Furthermore, cardiac evaluation and general anesthesia must be performed by experienced specialist pediatric cardiologists/anesthesiologists.

A high dental caries prevalence is observed in WBS individuals owing to hypercalcemia-induced enamel hypoplasia and hypomineralization, with concomitant delayed tooth eruption [18]. Anorexia and vomiting are other risk factors reported to be responsible for enhanced caries vulnerability [27]. Prevention of infection in the oral cavity is the best way to minimize dental problems, especially in vulnerable WBS individuals such as those with severe enamel hypoplasia, high dental caries incidence and severe cardiac conditions [18]. Intense preventive and dietary counseling must be organized for such individuals, particularly children. Fluoride mouthwash, topical fluoride applications, tooth brushing twice a day, oral water rinse after every feed, use of a dental floss once every night, regular quarterly professional prophylaxis, and pit and

Table V. Risk stratification for WBS undergoing procedures under general anesthesia.

Low risk	>20 Years of age, cardiac involvement limited to mild supravalvar or branch pulmonary artery stenosis, normal ECG, lacking renal artery involvement.
Moderate risk	Hypertension, supravalvar or branch pulmonary artery stenosis of moderately involvement, mild bilateral outflow tract obstruction, renal artery stenosis, renal dysfunction, ECG findings of QTc between 450 and 500 ms, lung/airway abnormalities, severe gastroesophageal reflux.
High risk	<3 Years of age, history of adverse cardiovascular event, presence of preprocedural arrhythmia, bilateral outflow tract obstruction of ≥ moderate severity, SVAS gradient of ≥40 mm Hg with concomitant left ventricular hypertrophy, involvement of coronary artery, thoracic aorta diffuse stenosis, ≥ moderate left/right ventricular hypertrophy, cardiac ischemic symptoms/ECG evidence,ECG findings of QTc ≥500 ms

ECG, Electrocardiogram; QTc, QT interval on ECG (corrected); SVAS, supravalvar aortic stenosis (Adapted from Collins *et al*. [26]).

fissure sealants are some of the preventive measures. Use of a powered toothbrush may be indicated for those with mental disabilities or those who have tooth brushing performed by caregivers [28].

Most WBS children exhibit varying degrees of anxiety and uncooperative behavior in the dental office. Behavior modification can be brought about through modulating sessions that use the basic behavior guidance techniques recommended by the American Academy of Paediatric Dentistry (AAPD) guidelines on behavior guidance for pediatric dental patients [29]. These guidelines recommend methods such as efficient communication with and communication guidance for the patient, tell-show-do technique, appropriate use of voice control, non verbal communication, use of positive reinforcement, distracting the patient, parental presence/absence and nitrous oxide/oxygen inhalation sedation to modulate child behavior positively and to gain cooperation for dental treatment [29].

Visual acuity may be affected to varying degrees in WBS patients. Inability to visualize the surroundings and operative equipment may increase the patients' anxiety, apprehension and fear of the unknown [30]. Patients may be allowed to have tactile stimulation by touching operative instruments, the dental chair, and take a tour of the dental office to acclimatize themselves to the surroundings since they have a better chance to overcome apprehension and fear of the unknown, at the same time forging a strong bond with the support staff at the dental office [18].

WBS patients exhibit a strong affinity towards music. This fact can be utilized to advantage at the dental office to gain cooperation from patients and assist in keeping them more relaxed during treatment, especially considering the hyperacusis associated with WBS patients. Allowing patients to use their headphones and listen to their choice of music is preferable in WBS patients. Furthermore, hyperacusis predisposes WBS patients to easy distraction during dental procedures making them vulnerable to mishaps from sudden involuntary movements while in the dental chair [31]. The dental chair operating light may be disturbing to WBS patients owing to photophobia and allowing them to wear a pair of sunglasses may assist in mitigating this issue [18].

Benefits of early dental evaluation and parental education cannot be understated in WBS patients, considering that dental caries and pulpal infection may increase the risk of serious complications due to congenital heart defects and the inherent risk of subacute bacterial endocarditis (SABE) [18]. A comprehensive radiographic examination must be undertaken to evaluate any dental anomalies and establish a treatment plan for restorative and orthodontic rehabilitation of patients [18].

Yamaguchi *et al*. have reported the treatment of a 4 year old WBS patient with isolated cleft palate who was followed up of 20 years [32]. They successfully completed non invasive procedures such as orthodontic treatment, invasive procedures such as maxillary anterior segmental distraction osteogenesis and dental implant supported prosthetic rehabilitation. They highlighted the fact that in WBS patients with minimal systemic compromise, acceptable mental abilities and cooperative behavior, oral healthcare provision could be carried out without untoward incidents. Orthodontic evaluation and treatment is advisable in WBS children as soon as their behavior allows cooperation. Primary and mixed dentition stages are preferable for eradication of mucogingival problems associated with anterior cross-bite and pseudo class III malocclusion [18].

Important information to remember in WBS patients is that they have an increased chance of developing impaired glucose tolerance with reduced insulin sensitivity, eventually progressing to type 2 diabetes mellitus [33]. Therefore, it would be prudent to recheck their glycemic levels before every dental appointment when spaced a few months to a year apart [34]. Urban *et al*. demonstrated with the use of electron microscopy, that elastin gene deletion in WBS resulted in reduced elastin fibre deposition and accumulation of abnormal elastin fibres in the skin [35]. This compromised the mechanical properties of the skin. It would be prudent to think that all facial incisions used to access jaw fractures such as condylar fractures may be avoided and treatment be completed by conservative methods such as maxillo-mandibular fixation. Similarly, it would be wise to avoid raising mucoperiosteal flaps in the oral cavity such as are used in third molar surgery, endodontic surgery and periodontal flap surgeries. The risk of wound dehiscence is greater in WBS patients.

The proceedings at the 15th professional conference on Williams Syndrome, 2016, provided guidelines for selection of the type of anesthesia for dental procedures [36]. The panel suggested that, since a private dentist's office would generally be unable to appropriately monitor patients during and after sedation (ECG, oxygen saturation), for procedures under conscious sedation, dental procedures (especially in WBS children) are best performed at a center with specialized expertise in anesthesia [36]. Therefore, low cardiac risk individuals (Tab. IV, Collins *et al*. [26]) are the only WBS subset of individuals who can safely be treated under local and/or behavioral treatment at the dental office. Adrenaline must not be used with local anesthesia in WBS patients [36]. Accordingly, mild risk individuals requiring sedation and moderate/high risk individuals are treated in a hospital setting only.

Presence of significant renal compromise may complicate oral healthcare in WBS patients. Constant blood pressure monitoring is advisable in light of the fact that hypertension is a risk factor for cardiac complications. Nephrotoxic drugs such as aminoglycosides and tetracyclines must be avoided [37]. Penicillins, cephalosporins and clindamycin are safe antibiotic choices. Paracetamol is the best drug for pain relief, although severe pain can be managed with codeine, even in an unmodified dose [37]. Aspirin and NSAIDs ate contraindicated in WBS patients with significant renal disease since they increase bleeding tendency and may contribute to deterioration of renal function [37]. If patients are on hemodialysis, dental procedures must be planned on the day following the dialysis. Local anesthetics may be safely used since they are eliminated from the hepatic route [37].

Renal disease also predisposes the WBS patient to bleeding tendencies due to anemia and platelet aggregation disorders [37]. Some WBS patients may also be on oral anticoagulants due to cardiac issues. International normalized ratio (INR) and a blood hemogram with coagulation time testing would be mandatory before any invasive procedure. Local hemostatic measures such as digital compression, cold applications, tranexamic acid mouthwash, cellulose sponges and sutures are generally sufficient to arrest local haemorrhage in patients with INR ≤ 2 [37]. In patients with INR >2, a nephrologist consultation to reduce the level to below 2 must be undertaken to plan dental procedures.

Conclusion

Considering the significant impediments to oral healthcare provision in WBS patients, prevention of oral infection seems to be the best strategy. Dietary counselling, periodic oral examinations, oral prophylaxis, and early recognition and treatment of dental problems can mitigate serious complications and risks involved in treating advanced oral infections in WBS patients. The choice of local anesthetia/sedation/general anesthesia for carrying out dental procedures in WBS individuals must be made considering the needs of the procedure, as well as the physiologic/mental abilities of the patient. A coordinated, multidisciplinary approach to oral healthcare could provide the patient with a healthy oral cavity, in a safe environment, which in turn would mean a healthier patient.

Conflict of interest

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