Multidisciplinary Management of Opitz G BBB Syndrome

S. Y. Parashar, MCh, P. J. Anderson, MD,* T. C. Cox, PhD,† N. McLean, MD,† and D. J. David, AC, MD*†*

Abstract: Opitz G BBB syndrome is a rare condition characterized by the 3 major anomalies of hypertelorism, cleft lip and palate, and hypospadias, although there may be other associated anomalies. The underlying genetic causes are complex and consist of both X-linked recessive and autosomal dominant forms of the disorder. Previously, there have been publications on the underlying genetics and case reports, but there have been few reports regarding the long-term outcome.

The aim in this study was to review the range of clinical presentation and evaluate outcomes of the multidisciplinary management of a cohort of patients with Opitz G BBB syndrome. In a 25-year period, 7 patients with Opitz G BBB syndrome were managed by the Australian Craniofacial Unit (ACFU), 5 male and 2 female. Most of the patients are now reaching skeletal maturity. Each one presented with a range of severity in the triad of hypertelorism, cleft lip and palate, and hypospadias anomalies. The males all exhibited the triad of anomalies, while the females both had hypertelorism, only 1 had isolated cleft palate, and neither had any genitourinary anomalies. Each patient underwent multidisciplinary assessment to make a treatment plan for staged management of different anomalies. Plan for surgical corrections of facial anomalies were performed according to the unit's protocol management of both hypertelorism and cleft lip and palate, but the presence of these coexisting anomalies required adjustment of the standard protocol of management of cleft lip and palate.

In conclusion, we recommend that patients with Opitz G BBB syndrome require careful evaluation, and management of the anomalies should be in a coordinated manner by a multidisciplinary team.

Key Words: Opitz syndrome, cleft lip and palate, hypertelorism, hypospadias, oculogenitolaryngeal

(*Ann Plast Surg* 2005;55: 402–407)

Opitz G BBB syndrome is a congenital condition characterized by a variable spectrum of anomalies that include the triad of hypertelorism, cleft lip and palate, and hypospadias. Other anomalies include laryngo-esophageal abnormalities, imperforate anus, cardiac defects, and developmental delay. John Opitz originally described this condition as separate clinical entities, G and BBB syndromes: the names derived from the first letter of the family names of the patients described in the initial report.[1,2] However, it is now widely recognized that the 2 original descriptions were variable presentations of a single entity.[3,4] The incidence of this condition remains unknown and is difficult to determine because of the marked variability in clinical presentation. This is highlighted by a number of reports where retrospective clinical evaluation and genetic testing have revealed multiple mutation-positive, mildly affected relatives of probands.[5]

The condition is peculiar in that it is genetically heterogenous, with both X-linked (Xp22.3) and autosomal (22q11.2) inheritance described.[4,5] A contribution from both chromosomes may explain some of the clinical variability, although other unknown factors affect clinical presentation. Mutations in the MID 1 gene on the X chromosome have been found responsible for the X-linked form of this disease, although the precise developmental consequences resulting from the loss of this gene is not completely understood.[5]

Recently, a review revealed that hypertelorism is the most common feature in patients, being present to some degree in all individuals of both sexes. Hypospadias was also found to be present in over 82% of affected males, while cleft lip and palate was less commonly seen, reportedly only 50% of cases.[5] A range of other craniomaxillofacial deformities has been reported in this condition and is shown in Table 1.[3] Previously, there have been few reports on the overall management and long-term follow-up.[6–9]

The aim in the present study was to review the clinical features in a cohort of patients with Opitz G BBB who are reaching skeletal maturity and evaluate the long-term results of surgical management.

METHODS

The departmental database was used to identify cases of Opitz G BBB syndrome, and case notes were retrieved, along with specific studies, including radiology and 3-dimensional computed tomographic reconstruction to assess the extent of the abnormality. Inclusion criteria selected only those cases where an experienced clinical geneticist confirmed the diagnosis.

Received October 28, 2004 and accepted for publication, after revision, May 24, 2005.

From the *Australian Craniofacial Unit, North Adelaide, South Australia and the †Australian Craniofacial Institute, associated with the University of Adelaide, Australia.

Reprints: S. Y. Parashar, MCh, Australian Craniofacial Unit, Women's and Children's Hospital, North Adelaide, South Australia 5006. E-mail: sanjayparashar2001@yahoo.com

ISSN: 0148-7043/05/5504-0402
DOI: 10.1097/01.sap.0000174355.56130.0a

TABLE 1. Anomalies Associated With Opitz G BBB Syndrome[3]

Craniofacial	
Head	Cranial asymmetry and prominences, midline furrow, widow's peak
Facial bones	Hypoplasia
Nose	Flattened bridge, anteverted nostrils, grooved nasal tip
	Nostril cleft
Eyes	Hypertelorism, telecanthus/epicanthal folds, strabismus, entropion, ptosis
Ears	Posterior rotation
	Abnormal modeling of helix
Oral structures	Cleft lip and palate, fused teeth/supernumerary teeth
	Bifid uvula, ankyloglossia/bifid tongue
	Short lingual frenulum
Urogenital	Hypospadias, vesicoureteric reflux
Respiratory	Stridor, aspiration pneumonia, atelectasis
	Bronchiectasis, laryngotracheal cleft
	Tracheo-oesophageal cleft
Cardiovascular	ASD/VSD/PDA/TOF
	Coarctation aorta
GIT	Upper tract malformation
	Esophageal motility, imperforate anus
Others	Inguinal hernia/pes cavus/deformed digits
	Midline brain anomalies, developmental delays

ASD, atrial septal defect; PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Hypertelorism and cleft lip and palate (CLP) were managed according to the unit protocol[10,11]; however, the protocol for the management of CLP was customized to deal with the management of the other associated anomalies.

RESULTS

The departmental database identified a total of 7 patients with Opitz G BBB syndrome in a 25-year period from 1980 to 2004. Of these, 5 were male and 2 female, with a current mean age of 15 years and average follow-up of 14 years. All underwent full multidisciplinary assessment with initial review by craniofacial surgeon, plastic surgeon, speech pathologist, pediatrician, pediatric surgeon, respiratory physician, and cardiologist due to the presence of multiple anomalies. Clinical genetic assessment was undertaken to establish a diagnosis, and patients were offered genetic testing. Basic radiology of skull and chest with CT scan and 3D reconstruction of the skull was performed to assess the deformity. A multidisciplinary planning was undertaken for each patient to establish treatment priority. Craniofacial anomalies were managed according to the ACFU protocol of hypertelorism and CLP.[10,11]

On reviewing the clinical presentation, all the males were found to have hypertelorism, facial cleft, and hypospadias. Both female patients had hypertelorism and 1 female had isolated cleft of the posterior palate, but none had genitourinary anomalies. All the patients had a wide range of clinical features. Case 7 was a mild presentation with hypertelorism, midface hypoplasia, and an associated cardiac anterior septal defect (Fig. 1A, B). Two patients were found to have MID1 gene error in X chromosome. In 4 other cases, no mutations were detected, and 1 declined testing.

The management of the anomalies of these patients was grouped in the triad of clinical features as follows.

Hypertelorism (Table 2 and Fig. 2A)

Hypertelorism was a consistent finding in all patients, and the bony interorbital distance (BIOD) was measured between the dacryons on a plain radiology of skull (Fig. 2B). Patients were grouped as mild, moderate, and severe hypertelorism on the basis of measurement. Six patients had mild and moderate, whereas 1 had severe, hypertelorism. All patients had epicanthal folds, and 2 had congenital unilateral ptosis. Three patients had congenital strabismus, and 1 acquired it following hypertelorism surgery. Two patients underwent ophthalmological correction. Four patients underwent surgery to correct the hypertelorism using box osteotomy technique preserving the cribriform plate recommended by Converse.[12] One patient required 2 procedures, a subcranial orbital osteotomy at age 5 and a box osteotomy at age 17. It was noted that there is a tendency for the cribriform plate to be low, which clearly needs to be borne in mind when planning corrective hypertelorism surgery. The pre- and postoperative BIOD were compared (Table 3). There were no significant complications following hypertelorism surgery, apart from anosmia and strabismus, which occurred on 1 occasion each.

Cleft Lip and Palate (Table 4 and Fig. 3A, B)

Out of 6 patients with cleft anomalies, 4 had bilateral complete cleft lip and palate, 1 had a unilateral complete lip and palate, and 1 patient had an isolated complete cleft of the palate. Three patients had their cleft management from birth in the ACFU, 2 patients entered the protocol at 2 and 4 years of age, respectively, and 1 patient was already skeletally mature when referred. Lip repair was performed at the average age of 6 months. This is a delay of 3 months' time of the

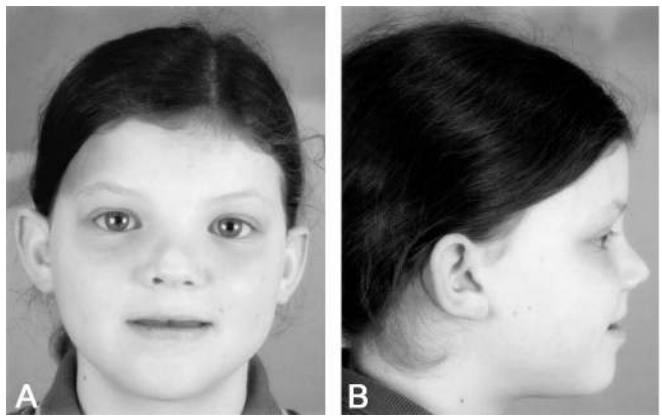

FIGURE 1. A, Eleven-year-old female with Opitz G BBB syndrome showing mild hypertelorism and nasal deformity. B, Same patient in a profile view showing midface hypoplasia.

TABLE 2. Hypertelorism

Case	Hypertelorism	Procedure	Age at Surgery
1	Mild	Box osteotomy/canthoplasty/ptosis correction	6 y
2	Moderate	Box osteotomy/canthoplasty	5 y
3	Moderate	Subcranial osteotomy and box osteotomy/canthoplasty	7 y and 17.3 y
4	Mild	Young	
5	Moderate	Box osteotomy/canthoplasty	5.2 y
6	Severe	Lost to follow-up	
7	Mild	Young	

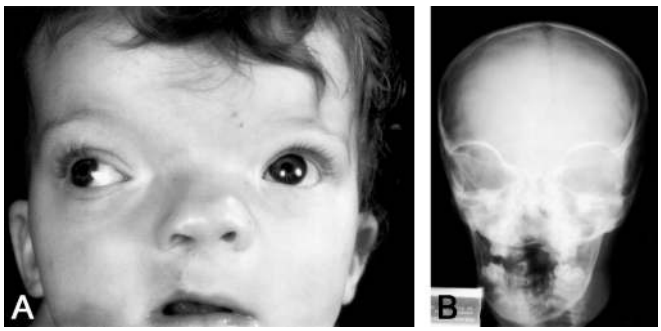

FIGURE 2. A, Severe hypertelorism and telecanthus in a 1-year-old child. B, Plain radiology of skull (AP view) for measurement of BIOD.

TABLE 3. Bony Interorbital Distance (BIOD)

Case	Preoperative BIOD	Postoperative BIOD
1	31 mm	29 mm
2	38 mm	31 mm
3	37 mm	22 mm

current CLP protocol.[10] A Wardill-Kilner type of palate repair[13] was performed in all cases, along with myringotomy and insertion of grommets at the average age of 14 months. The delay in the timing of surgery was due to the presence of respiratory, cardiac, urologic, and feeding problems that required prolonged hospitalization. Alveolar bone grafting was performed at the time of mixed dentition, similar to other patients in CLP protocol. A total of 4 out of 6 patients with CLP required superior flap pharyngoplasty at the average age of 12 years after detection of VPI on serial speech evaluation and nasoendoscopic assessment. This highlights the importance of multidisciplinary assessment throughout the growth period. Two patients required Abbé flaps at the age of 14 and 17 years, respectively, to correct horizontal lip shortness and improve the nasolabial profile when they were adult.

Hypospadias (Table 5 and Fig. 4)

All of the males had hypospadias; 1 was perineal, 3 of penoscrotal, and 1 coronal type. Female patients did not have any genitourinary anomalies. All had a multistage repair, 2 developed fistulae requiring further surgery, and 1 had a persistent chordee. One of the patients had upper genitourinary abnormality that required ureteric surgery.

In addition to the triad of deformities, there were other associated facial anomalies. Midface deformity (Table 6), including midface hypoplasia, was present in all patients, including 1 patient who had no cleft deformity. Hypoplastic zygoma (3 out of 7 patients), depressed nasal bridge, and upturned nose (4 out of 7 patients) were also associated midface deformities.

Three patients underwent malar augmentation, 4 patients had open rhinoplasty with cantilever costochondral bone grafts, and 2 required Le Fort I maxillary advancement procedure, and these were performed after reaching skeletal maturity. One patient had good facial growth and was managed by orthodontics alone, without the need of maxillary osteotomy (Figs. 5–9). Cranial asymmetry and frontal bossing (2 patients), ear deformity, including low-set and rotated ears (3 patients), and tongue-tie (3 patients) were also identified.

Other anomalies that required appropriate management included airway problems (stridor and laryngomalacia), gastrointestinal abnormalities (imperforate anus and esophageal reflux), and cardiac diseases (PDA, ASD, VSD).

TABLE 4. Cleft Lip and Palate (CLP): Pathology and Age at Repair

Case	Pathology	Lip Repair	Palate Repair	Alveolar Bone Graft	Pharyngoplasty
1	Bilateral complete CLP	8 mo	20 mo	12 y	9 y
2	Unilateral complete CLP	5 mo	9 mo	14.5 y	7.5 y
3	Bilateral complete CLP	3 mo	10 mo	12 y	5.3 y
4	Bilateral complete CLP	7 mo	12 mo	Awaiting	–
5	Bilateral complete CLP	7 mo	10 mo	17.6 y	26.2 y
6	Isolated Cleft Palate	–	20 mo	–	–
7	No cleft	–	–	–	–

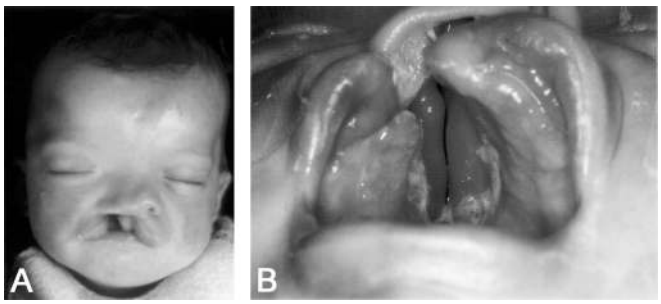

FIGURE 3. A, Five-month-old male baby showing unilateral cleft lip deformity. B, Same child showing unilateral cleft palate deformity.

TABLE 5. Hypospadias and Its Severity

Case	Hypospadias: Perineal	Hypospadias: Penoscrotal Penile	Hypospadias: Coronal	Other Anomalies
1	+			
2		+		
3			+	
4		+		VUR and UTI-Ureteric reimplantation
5		+		

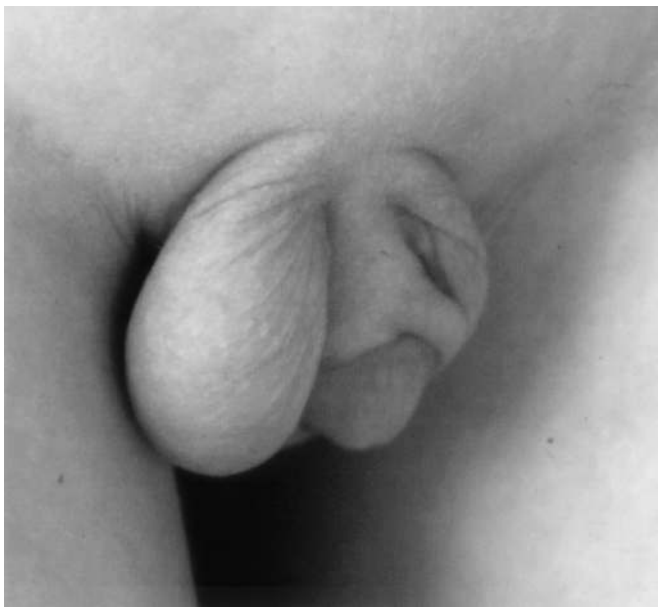

FIGURE 4. Perineal hypospadias with bifid scrotum.

All patients were regularly reviewed throughout the growth period, and the definitive correction, including orthognathic and soft-tissue refinement surgery, was performed after skeletal maturity.

DISCUSSION

Opitz G BBB syndrome is a condition with variable clinical presentation. It varies in severity from mildly affected (Fig. 1) to severely affected patients and may have multiple associated congenital anomalies. The severity may be such that neonatal death and infant mortality may occur.[3,14] Most of the anomalies in this disorder affect the midline, suggesting that the genetic mutation exerts its effect predominantly on midline morphogenetic processes.[2] Investigations into the underlying genetic defects and the pathobiochemistry of this syndrome have identified that development of the ventral midline is a complicated multistep process.[15]

Many synonyms are attached with the Opitz G BBB syndrome, including Opitz oculogenitolaryngeal syndrome,[16] Opitz syndrome,[1] and G syndrome.[17] Marked overlap of the phenotype presentations, the same inheritance pattern, and male preponderance of these differently named syndromes suggested unification; hence, a compound name, Opitz G BBB syndrome, was proposed.[16]

The triad of deformity had variable range of presentation. Hypertelorism was present in all of the patients in this series. It has been reported that hypertelorism is a common denominator in males with identified MID1 mutations.[4,5] BIOD measured on plain skull radiology was used to grade hypertelorism.[18] All the patients in this study had hypertelorism, and these were grouped into 3 categories to highlight the variability. Tessier's classification[12] for the severity of hypertelorism could not be used because it has been described for adult population, and larger data are required for age- and gender-matched classification as described by Mulliken.[19]

TABLE 6. Surgery of the Midface

Case	Malar Augmentation	Rhinoplasty	Midface Advancement
1	+	+	−
2	−	+	−
3	+	+	+
4	−	−	−
5	+	+	+
6	−	−	−
7	−	−	−

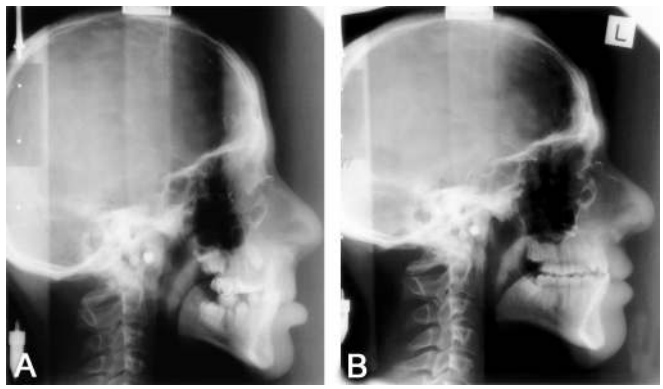

FIGURE 5. A, Lateral cephalogram in a 6-year-old male showing skeletal class III jaw relationship. B, Lateral cephalogram of the same patient after skeletal maturity at the age of 24 years.

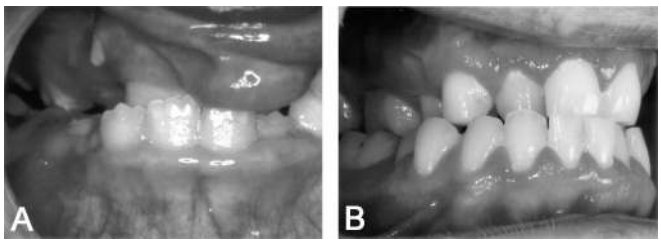

FIGURE 6. A, Occlusal relationship prior to orthodontics in the same patient in Figure 5. B, Dental relationship after completion of orthodontics management at the age of 24 years.

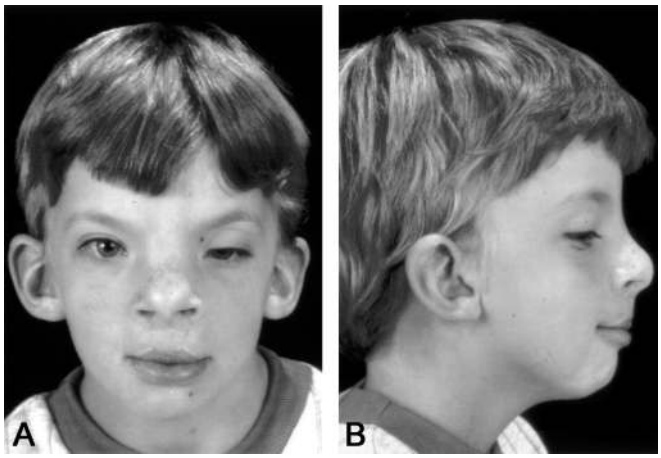

FIGURE 7. A, Frontal view of a 6-year-old male showing bilateral CLP, hypertelorism, and unilateral ptosis. B, Profile view of the same patient in Figure 7A.

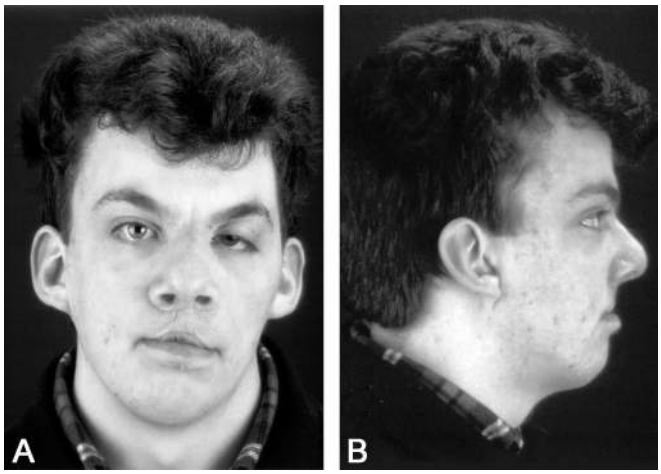

FIGURE 8. A, Same patient at age of 16 years after several reconstructive procedures. B, Profile view at 16 years of age.

Three patients had mild (30.1–34.9 mm) hypertelorism, 3 had moderate (35–39.9 mm), and 1 patient had severe (>40 mm) hypertelorism (Table 2) again showing the range of severity. This required a range of management strategy. Postoperatively, BIOD measurement was compared and showed improvement in all patients. All patients were evaluated by an ophthalmologist as a part of multidisciplinary assessment.

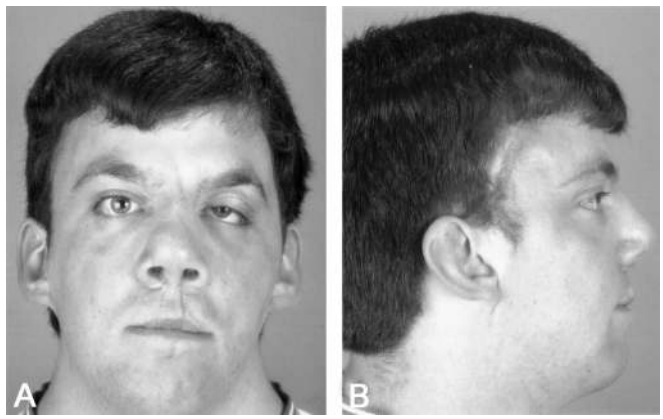

FIGURE 9. A, Same patient after skeletal maturity (24 years) showing good facial growth. B, Profile view of the same patient showing good skeletal jaw relationship after orthodontics only.

Cleft lip and palate was present in 86% in this series, and it ranged in severity from isolated cleft palate to bilateral complete cleft of lip and palate. In one report, cleft palate was seen in 34%[20]; in another report, 34% of patients had intraoral abnormalities.[7] In this series, the patients were managed according to the CLP protocol. However, the timing had to be altered to manage associated anomalies whose treatment was planned by multidisciplinary team. Notably, 4 out of 6 patients with cleft required pharyngoplasty, which is not commonly undertaken in our nonsyndromic isolated cleft palate population, possibly indicating the severity of midline deficiency.

Hypospadias was present in 100% of the male patients, whereas females had no genital anomalies, which is similar to the report of Peeden et al.[20] The types varied from distal coronal to proximal perineal with bifid scrotum, and 1 patient had associated ureteral anomaly. This contrasts the report of Peeden et al,[20] where the site is not recorded. Multistaged reconstruction was performed in all the patients.

There is a range of other craniofacial anomalies present in Opitz G BBB syndrome,[1,3] including cranial asymmetry, ear malformations, midface hypoplasia, and nasal deformity. In this study, midface hypoplasia was present in all patients, including 1 without any cleft. The common procedures performed in these patients are augmentation rhinoplasty, malar augmentation, and Le Fort I maxillary advancement. One patient in this series with bilateral CLP had good facial growth throughout the developmental period and achieved a good facial balance with orthodontics alone, as shown in Figures 5 and 6.

The associated anomalies previously described include neuromuscular defects of the esophagus, imperforate anus, mental retardation and dysphagia with aspiration, laryngotracheoesophageal anomalies, central nervous system malformations, and cardiac anomalies.[2,21]

In this series, 51% had gastrointestinal anomalies, whereas 43% had cardiac anomalies. Four patients (57%) had

neonatal respiratory illnesses causing long periods of hospitalization, while only 1 patient had laryngomalacia. Presence of these multiple diseases was the reason for delay in cleft repair. These visceral abnormalities are the cause of high morbidity and mortality in patients with Opitz G BBB syndrome.[2,14]

In conclusion, the condition has a triad of clinical features with variable severity, which have been highlighted in this series. Within the triad, the features have a range of presentation that may be associated with other anomalies. This results in our recommendation that management by multidisciplinary team is required for customized treatment and coordinated care.

Finally, we propose a management strategy (Table 7) recommending that patients with Opitz G BBB syndrome are best treated in regional craniomaxillofacial centers so that an appropriate customized management protocol can be followed for each individual patient.

TABLE 7. Protocol for the Management of Opitz G BBB Syndrome

Period of Growth	Management
Neonatal period	Multidisciplinary assessment by craniofacial surgeon, ENT, ophthalmologist, pediatrician, pediatric urologist, cardiologist, respiratory physician, speech pathologist, and clinical geneticist
Childhood period	Hypertelorism: ophthalmology assessment
	Neurosurgery assessment
	Surgery timing influenced by the developing dentition
	CLP: lip repair and myringotomy, palate repair
	Speech review
	Dental and orthodontic evaluation
	Hypospadias: urological assessment
	3-Staged reconstruction
	Management of cardiac, respiratory and gastrointestinal anomaly if indicated
Adulthood	Orthognathic and soft tissue refinement surgery

ACKNOWLEDGMENTS

We would like to express our special thanks to Louise Netherway (Research Officer) and Christopher Sprod (Clinical Photographer) for their support and assistance in preparing this manuscript. This paper was presented at the Fifth Asian Pacific Craniofacial Association conference in Seoul, Korea, on October 4, 2004.

REFERENCES

1. Cappa M, Borrelli P, Marini R, et al. The Opitz syndrome: a new designation for the clinically indistinguishable BBB and G syndromes. *Am J Med Genet*. 1987;28:303–309.
2. Opitz JM. Editorial comment: G syndrome (hypertelorism with oesophageal abnormality and hypospadias, or hypospadias-dysphagia, or Opitz-Frias or Opitz-G syndrome): perspective in 1987 and bibliography. *Am J Med Genet*. 1987;28:275–285.
3. Verloes A, Le Merrer M, Briard ML. BBBG syndrome or Opitz syndrome: new family. *Am J Med Genet*. 1989;34:313–316.
4. Cox TC, Allen LR, Cox LL, et al. New mutations in MID1 provide support for loss of function as the cause of X-linked Opitz syndrome. *Hum Mol Genet*. 2000;9:2553–2562.
5. So J, Opitz JM, Cox T, et al. Mild phenotypes in a series of patients with Opitz GBBB syndrome with MID1 mutations. *Am J Med Genet*. In press.
6. Bolsin SN, Gillbe C. Opitz-Frias syndrome: a case with potentially hazardous anaesthetic implications. *Anaesthesia*. 1985;40:1189–1193.
7. Brooks JK, Leonard CO, Coccaro PJ Jr. Opitz (BBB/G) syndrome: oral manifestations. *Am J Med Genet*. 1992;43:569–601.
8. Howell L, Smith JD. G syndrome and its otolaryngologic manifestations. *Ann Otol Rhinol Laryngol*. 1989;98:185–190.
9. Farndon PA, Donnai D. Male to male transmission of the G syndrome. *Clin Genet*. 1983;24:446–448.
10. Schnitt DE, Agir H, David DJ. From birth to maturity: a group of patients who have completed their protocol management, part I: unilateral cleft lip and palate. *Plast Reconstr Surg*. 2004;113:805–817.
11. David D. The Australian cranio-facial unit 1974–1994. *Aust J Otolaryng*. 1994;1:566–576.
12. Tessier P. Orbital hypertelorism, 1: successive surgical attempts, material and methods, causes and mechanism. *Scand J Plast Reconstr Surg*. 1972;6:135–155.
13. Choudhary S, Cadier MA, Shinn DL, et al. Effect of Veau-Wardill-Kilner type of cleft palate repair on long-term midfacial growth. *Plast Reconstr Surg*. 2003;111:576–582.
14. Einfeld SL, Fairley MJ, Green BF, et al. Sudden death in childhood in a case of the G syndrome. *Am J Med Genet*. 1987;28:293–296.
15. Schweiger S, Schneider R. The MID1/PP2A complex: a key to the pathogenesis of Opitz BBB/G syndrome. *Bioessays*. 2003;25:356–366.
16. Sedano HO, Gorlin RJ. Opitz oculo-genital-laryngeal syndrome (Opitz BBB/G compound syndrome). *Am J Med Genet*. 1988;30:847–849.
17. Opitz JM, Frias JL, Gutenberg JB, et al. The G syndrome of multiple congenital anomalies. *Birth Defects*. 1969;5:95–98.
18. Cohen MM Jr, Richieri-Costa A, Guion-Almeida ML, et al. Hypertelorism: interorbital growth, measurements, and pathogenetic considerations. *Int J Oral Maxillofac Surg*. 1995;24:387–395.
19. Tan ST, Mulliken JB. Hypertelorism: nosologic analysis of 90 patients. *Plast Reconstr Surg*. 1997;99:317–327.
20. Peeden JN, Wilroy RS Jr, Summitt RL Jr. The telecanthus-hypospadias syndrome revisited [abstract]. *Proc Greenwood Genet Center*. 1983;2:131–132.
21. Guion-Almeida ML, Richieri-Costa A. CNS midline anomalies in the Opitz G/BBB syndrome: report on 12 Brazilian patients. *Am J Med Genet*. 1992;43:918–928.