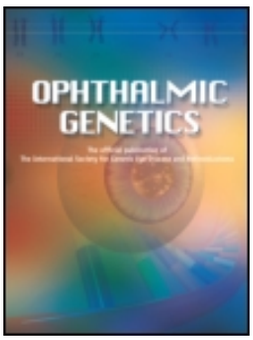

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RESEARCH REPORT

Ocular Features in 16 Brazilian Patients with Williams-Beuren Syndrome

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ABSTRACT

Objectives: Williams-Beuren Syndrome (WBS) is a multisystem disorder caused by the deletion of contiguous genes on chromosome 7q11.23. Ophthalmologic abnormalities and deficits in visual motor integration are important features of WBS. Here we describe our experience with Brazilian WBS patients and their ophthalmologic features.

Methods: Sixteen patients with confirmed WBS went through thorough ophthalmologic examination.

Results: The most frequent ocular findings in our group of patients were stellate iris pattern (81.2%), hyperopic astigmatism (50%), hyperopia (37.5%), tortuosity of retinal vessel (37.5%) and strabismus (18.7%).

Conclusions: This is the second report of ophthalmologic abnormalities in a group of Brazilian individuals with WBS. It is extremely valuable that specific populations are studied so that clinical diagnosis can be refined and management of patients can be driven to the most common presentations of the disease.

Keywords: 7q11.23, microdeletion, ocular features, Williams-Beuren syndrome

INTRODUCTION

Williams-Beuren Syndrome (WBS – OMIM #194050)[1] is a multisystem disorder caused by the deletion of 26–28 contiguous genes, including elastin gene (*ELN*), on chromosome 7q11.23.[2] Its prevalence is estimated as 1/7500[3] and its classic form includes: dysmorphic facial features (100%), intellectual disability (75%), cardiovascular disease [most commonly supravalvular aortic stenosis (80%)], infantile hypercalcemia (15%) and a unique personality and cognitive profile (90%).[4,5] Ophthalmologic abnormalities and deficits in visual motor integration are common and important features of WBS.[5] Stellate iris pattern occurs in 70% of WBS patients and is one of the facial features in a diagnostic scoring method proposed by the American Academy of Pediatrics (AAP)[4] in order to establish clinical diagnosis. Strabismus (usually esotropia) typically affects 50% of infants and it is also present at AAP's diagnostic scoring table. Hyperopia is present in 50% of individuals and tortuosity of retinal vessels is reported in 20%.[5]

However, there are differences in clinical presentations of well delineated syndromes (such as WBS) in distinct populations.[6–9] Brazilians, being one of the most heterogeneous populations in the world due to more than 5 centuries of interethnic crosses between Europeans, Africans and Amerindians,[10] must be studied in order to determine their own most prevalent clinical features in a given disease. To the best

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of our knowledge, the only article of ocular features in Brazilian patients with WBS was published by Sugayama and colleagues in 2002.[11]

Here we describe an extensive range of ophthalmologic features in 16 Brazilian patients tested positive for WBS using a novel diagnostic method developed in Brazil.

MATERIAL AND METHODS

Sixteen patients with WBS were evaluated by an experienced ophthalmologist after being referred to a public genetic center in Minas Gerais, Brazil. Medical charts of all patients were analyzed; clinical history was obtained through parents and/or caregivers. The research protocol was approved by Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais. All parents signed informed consent forms. Thorough ophthalmologic examination including best correct visual acuity, anterior segment biomicroscopy, ceratometry, tonometry, indirect binocular ophthalmoscopy and fundus fotography was performed.

WBS was confirmed by Fluorescent in situ Hybridization (FISH) in four cases as described.[12] In the remaining 12 patients, WBS was detected as outlined in Stofanko and co-authors (2013).[13] Briefly, WBS patients were tested using a combination of PCR-based methods including the novel Microdeletion/Microduplication Quantitative Fluorescent PCR (MQF-PCR), loss of heterozygosity of four polymorphic microsatellites and Real-Time quantitative PCR as described by Stofanko and co-authors (2013).[13] Loss of heterozygosity of *ELN* and *LIMK1* was confirmed in all cases.

RESULTS

Out of 16 patients, 10 were female (62.5%) and 6 were male (37.5%). Mean age was 17.4 years (median age: 15.7), ranging from 5–40 years. All patients had intellectual disability and developmental delay. Clinical features, such as facial dysmorphisms, cardiovascular abnormalities, cognitive and behavioral profile, were typical of WBS (data not shown). The most frequent ocular findings are summarized in Table 1 and a complete list can be found in Table 2.

Strabismus was observed in three of our patients (18.7%); all had esotropia (one small-angle, one medium-angle, and one intermittent esotropia). One patient had cataract, one had epicanthal folds, one had a subconjunctival cyst, one had epiphora and one had suspected glaucoma (6.2%, each).

Anterior segment biomicroscopy revealed 13 patients (81.2%) with stellate iris pattern (Figure 1A), 1 with floccular opacities, one with suspected megalocornea (along with increased disc excavation and intraocular pressure), one with ocular asymmetry and one with keratoconus (KTCN) – 6.2%, each. As can be observed, some patients had more than one ocular feature (Table 2).

TABLE 1. Most frequent ocular findings.

Ocular findings	Present study (%)	Winter 1996[19]	AAP 2001[4]	Sugayama 2002[11,*]
Stellate iris pattern	81.2	74	NM	50
Visual acuity 20/20	73.3	NP	NM	NP
Hyperopic astigmatism	50.0	NP	NM	NP
Hyperopia	37.5	NP	50	NP
Tortuous retinal vessels	37.5	22	NM	50
Ceratometry ≥45.00	35.7	NP	NM	NP
Strabismus	18.7	54	50	50
Optic disk hypoplasia	12.4	NP	NM	6

*Only FISH-positive patients included. NM, not mentioned; NP, not performed.

Visual acuity was measured in all but one patient. Eleven patients (73.3%) had 20/20 best corrected visual acuity in both eyes (OU, *oculus uterque*), three (20%) had acuity of 20/30 in OU and one had 20/200 acuity in his left eye (LE) [in his right eye (RE), visual acuity was worst than 20/400].

Ceratometry was performed on OU in 13 subjects and was impracticable in the RE of the KCTN's patient. Medium ceratometry values were equal or greater than 45.00 in the RE of three patients (23.1%) and in the LE of five individuals (35.7%).

The most frequent refraction error in our sample was hyperopic astigmatism, with a prevalence of 50%. Hyperopia was found in six individuals (37.5%); mild astigmatism and irregular astigmatism were observed in one patient each (6.2%).

Ocular tonometry was normal in all patients. Seven individuals (43.7%) had tonometry values of 12 mmHg on OU. Tonometry values ranged from 10–16 mmHg.

Indirect binocular ophthalmoscopy revealed normal vitreous, macula and choroid in all patients. Fifteen patients (93.7%) had normal color optic disc, one (6.2%) had increased excavation, two (12.4%) had optic disk hypoplasia. Retinal examination showed normal caliber vessels in 10 patients (62.5%) and tortuous vessels in six individuals (37.5%) (Figure 1B). Fourteen patients (87.5%) had normal fundus. One patient (6.2%) had peripheral retinal degeneration.

All patients with ophthalmologic abnormalities were treated as usual.

DISCUSSION

To the best of our knowledge, this is the second report of ophthalmological findings in a population of Brazilian WBS patients. The first article of ocular features in Brazilian patients with WBS was published by Sugayama and colleagues in 2002.[11] The authors

TABLE 2. All ocular findings in 16 Brazilian WBS patients.

Patient	Sex	Age	Other Ophthalmol. findings	Biomicroscopy	Visual acuity RE	Visual acuity LE	Refraction errors	Tonometry	Papila	Vessels	Retina	Medium Ceratometry RE	Medium Ceratometry LE
1	F	34y3m	Cataract	SIP	20/30	20/30	Hyperopic astigmatism	12 OU	Optic disk hypoplasia	N	N	NP	NP
2	F	5y1m	Epicanthal folds	SIP	*	*	Hyperopia	N (bidigital)	N	T	N	45.00	45.00
3	F	21y9m	Subconjunctival cyst	SIP	20/20	20/20	Hyperopic astigmatism	14, 13	N	N	N	42.50	42.50
4	M	9y6m	–	SIP	20/20	20/20	Hyperopia	12 OU	N	N	Peripheral degeneration	44.75	45.25
5	F	5y5m	–	SIP	20/20	20/20	Hyperopia	10 OU	N	T	N	45.00	45.50
6	M	9y1m	–	SIP	20/20	20/20	Hyperopic astigmatism	12 OU	Optic disk hypoplasia	N	N	41.50	41.25
7	M	15y6m	–	SIP	20/20	20/20	Hyperopic astigmatism	14 OU	N	T	N	42.50	42.50
8	M	15y11m	–	SIP, cataract, floccular opacities	20/20	20/20	Hyperopic astigmatism	14 OU	N	T	N	43.75	43.50
9	F	14y5m	Epiphora	SIP	20/20	20/20	Mild astigmatism	IM	N	T	N	43.25	43.00
10	F	15y11m	Glaucoma?	Megalocornea?	20/20	20/20	Hyperopia	16 OU	Increased excavation	N	N	41.25	40.25
11	F	14y1m	–	SIP	20/20	20/20	Hyperopia	12 OU	N	N	N	45.25	45.75
12	M	16y7m	Strabismus	SIP	20/30	20/30	Hyperopic astigmatism	12 OU	N	N	N	41.50	42.50
13	F	23y6m	–	SIP	20/20	20/20	Hyperopic astigmatism	12 OU	N	T	N	42.25	43.00
14	F	14y11m	Strabismus	Ocular asymmetry	20/30	20/30	Hyperopic astigmatism	14 OU	N	N	N	NP	NP
15	F	18y6m	Strabismus	SIP	20/20	20/20	Hyperopia	12 OU	N	N	N	43.75	43.75
16	M	40y9m	KTCN	KTCN	20/400	20/200	Irregular astigmatism	14, 12	N	N	N	IM	48.00

y: years; m: months; *: patient with absent speech; -: Absent; NP: Not Performed; SIP: Stellate Iris Pattern; N: Normal, RE: Right Eye; LE: Left Eye; OU: *oculus uterque*; KTCN: Keratoconus; IM: Impracticable; T: Tortuous Vessels. Vitreous, macula and choroid were normal in all patients.

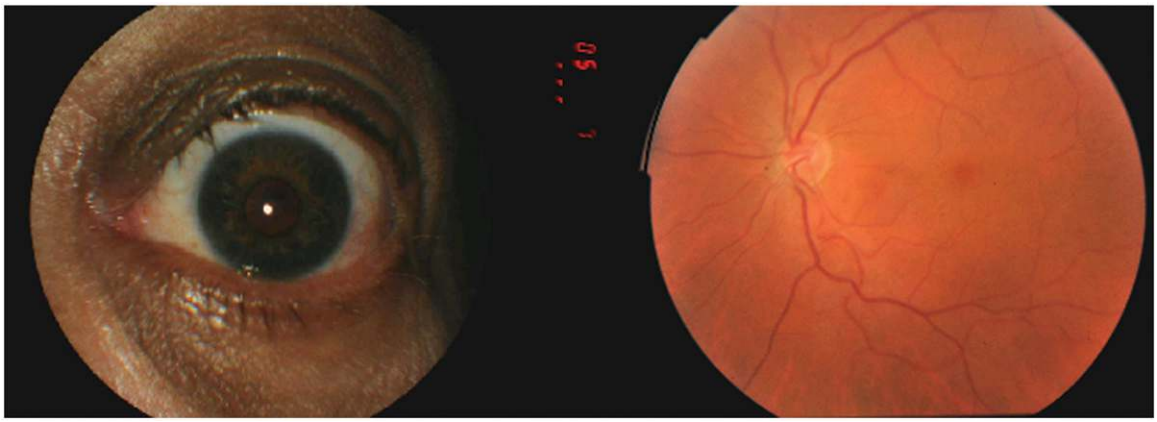

FIGURE 1. Images of (left) stellate iris pattern and (right) tortuous retinal vessels.

reported a limited number of ocular features in 17 patients tested positive for the 7q11.23 deletion using the standard LSI ELN FISH probe (Vysis, Inc.). Unfortunately, they included results of three cases that were not hemizygous for the LSI ELN probe and did not perform additional tests aimed at delineation of the WBS deletion interval. Despite showing most of the clinical symptoms of WBS (apart from cardiopathy), these cases should be considered as atypical cases of WBS, which may have resulted in misleading overall conclusions by Sugayama and co-authors (2002).[11] This work was followed by studies on cardiovascular abnormalities, renal and urinary findings, voiding-dysfunction, cognitive and behavioral phenotype, body mass index and anthropometric measurements.[14–18] However, no other report of ophthalmologic findings in a Brazilian population has been published.

Here we present an extensive set of ophthalmologic data for 16 patients positive for 7q11.23 deletion, out of which 12 patients were diagnosed using a molecular detection method developed for the public healthcare system in Brazil and four patients diagnosed through FISH. All patients studied share typical clinical symptoms of WBS and upon molecular testing showed hemizygous deletion at the WBS critical region. The most frequent ocular findings in our group of patients were stellate iris pattern (81.2%), hyperopic astigmatism (50%), hyperopia (37.5%), tortuosity of retinal vessel (37.5%) and strabismus (18.7%). Table 1 shows a comparison between our findings and data from previous reports.

Stellate iris pattern is usually found in 74% of WBS patients[19] with slit lamp examination (which is the gold standard test to detect such feature) and is a manifestation of hypoplasia and coarse architecture of the iris stroma.[5,20] Our rate was slightly higher when compared to the overall prevalence and much higher than Sugayama and colleagues (2002) who found stellate iris pattern in 50% of their FISH-positive patients.[11]

The most common refraction error found in WBS patients is hyperopia with a frequency of 50%.[4] We found hyperopia in 37.5% of our patients. Differently from other reports, the most frequent refraction error in our sample was hyperopic astigmatism, with a prevalence of 50%.

Strabismus is a common feature of WBS and was observed in 18.7% of our patients. Sugayama and colleagues (2002)[11] found strabismus in 50% of their FISH-positive patients, a similar rate found in other reports.[4,5,19] Since strabismus is more frequent in childhood, there is a possibility that our older mean age of 17.4 years (median age of 15.7) may be the reason for a low rate of squint. The most frequent form of strabismus in WBS is esotropia[19] and our data is not different from most reports.

Tortuosity of retinal vessels was found in 37.5% of our patients, which has been previously described.[5,11,19] This abnormality is probably related to elastin arteriopathy, which is an important aspect of WBS pathogenesis.[19]

One patient had visual acuity of 20/200 associated with KTCN. He also had a history of acute KTCN on his RE. KTCN is not regularly described as part of WBS. To our knowledge, this is the third case of KTCN associated with WBS.[21]

WBS is a microdeletion syndrome and 26–28 genes are usually deleted at 7q11.23 region. As discussed, some of the ophthalmological findings of WBS patients can be associated with *ELN* haploinsufficiency, the most important deleted gene in WBS that encondes elastin. However, we believe that an association between *LIMK1* and KTCN is possible.[21] The fact that we found 35.7% of subjects with ceratometry equal or greater than 45.00 in at least one eye can be suggestive that KTCN must be investigated on a regular basis in WBS patients, since values above 46.00 are suggestive of KTCN.

The majority of our patients had normal color optic disc (93.7%) and normal fundus (87.5%). Two had optic disk hypoplasia. Sugayama and co-authors (2002)[11] also found one WBS patient with optic

disk hypoplasia. One patient, a 9-year-old male, had peripheral retinal degeneration. We found no other reports of retinal degeneration in WBS patients.

One patient, a 34-year-old female, had cataract. Another patient, a 15-year-old male, had floccular opacities suggestive of cataract. Cataracts have been reported in adults with WBS.[22] Glaucoma was suspected in a patient with increased papilla excavation. And another patient had megalocornea. These findings are uncommon in WBS patients. However, they are relatively frequent in the general population. One patient had epiphora and narrowing of lacrimal duct which have been previously reported.[2] Two patients had ocular dysmorphisms usually found in WBS individuals: epicanthal folds and ocular asymmetry due to facial asymmetry.[5]

Yau and colleagues (2004)[6] stated that most published studies on WBS included only patients from western countries and that was the reason why the authors wanted to describe clinical characteristics of WBS in the Chinese population. They hypothesized that, among other reasons, some of the discrepancies they observed could reflect a genuine ethnic difference in genetic background that plays a role in modifying the phenotypic manifestation of the microdeletion. Brazilians, being one the most heterogeneous populations in the world,[10] must be studied in order to determine their own most prevalent clinical features in a given disease.

We believe that our extensive evaluation of ocular findings in patients with WBS has contributed to an increase in clinical expertise resulting in better management of patients. We propose ophthalmologic evaluation at time of diagnosis to be mandatory for every individual with suspected WBS and follow-up should be based on specific findings.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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REFERENCES

1. Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 194050: Date last edited: 07/12/2013. World Wide Web URL: http://omim.org/
2. Pober BR. Williams-Beuren Syndrome. N Engl J Med 2010; 362:239–252.
3. Strøme P, Bjornstad P, Ramstad K. Prevalence estimation of Williams syndrome. J Child Neurol 2002;17:269–271.
4. American Academy of Pediatrics (Committee on Genetics). Health Care Supervision for Children with Williams Syndrome. Pediatrics 2001;107:1192–1204.
5. Morris CA. Introduction: Williams Syndrome. Am J Med Genet C Semin Med Genet 2010;154C:203–208.
6. Yau EKC, Lo IFM, Lam STS. Williams-Beuren syndrome in the Hong Kong Chinese population: retrospective study. Hong Kong Med J 2004;10:22–27.
7. Figueroa JR, Rodriguez LMO, Hach JLP, et al. Cardiovascular spectrum in Williams-Beuren syndrome. Tex Heart Inst J 2008;35:279–285.
8. May PA, Gossage JP, Smith M, et al. Population differences in dysmorphic features among children with fetal alcohol spectrum disorders. J Dev Behav Pediatr 2010;31: 304–316.
9. Patil, SJ, Madhusudhan BG, Shah S, et al. Facial phenotype at different ages and cardiovascular malformations in children with Williams-Beuren syndrome: a study from India. Am J Med Genet Part A 2012;158A:1729–1734.
10. Parra, FC, Amado, RC, Lambertucci, JR, et al. Color and genomic ancestry in Brazilians. PNAS 2003;100:177–182.
11. Sugayama SMM, Sá LCF, Abe KT, et al. Anormalidades oculares em 20 pacientes com síndrome de Williams-Beuren. Pediatria 2002;24:98–104.
12. Ewart AK, Morris CA, Atkinson D, et al. Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. Nat Genet 1993;5:11–16.
13. Stofanko M, Gonçalves-Dornelas H, Cunha OS, et al. Simple, rapid and inexpensive quantitative fluorescent PCR method for detection of microdeletion and microduplication syndromes. PLoS ONE 2013;8:e61328.
14. Sugayama SMM, Moisés RL, Wagenfur J, et al. Williams-Beuren Syndrome. Cardiovascular abnormalities in 20 patients diagnosed with fluorescence in situ hybridization. Arq Bras Cardiol 2003;81:468–473.
15. Sugayama SMM, Koch VHK, Furusawa EA, et al. Renal and urinary findings in 20 patients with Williams-Beuren syndrome diagnosed by fluorescence in situ hybridization (FISH). Rev Hosp Clin Fac Med S Paulo 2004;59:272–277.
16. Sammour ZM, Gomes CM, Duarte RJ, et al. Voiding-dysfunction and the Williams-Beuren Syndrome: a clinical and urodynamic investigation. J Urol 2006;175: 1472–1476.
17. Teixeira MCTV, Monteiro CRC, Velloso RL, et al. Fenótipo comportamental e cognitivo de crianças e adolescentes com síndrome de Williams-Beuren. Pró-Fono Revista de Atualização Científica 2010;22:215–220.
18. Nogueira RJN, Zimmerman LF, Moreno YMF, et al. Anthropometric and body-mass composition suggests an intrinsic feature in Williams-Beuren syndrome. Rev Assoc Med Bras 2011;57:681–685.
19. Winter M, Pankau R, Amm M, et al. The spectrum of ocular features in the Williams-Beuren syndrome. Clin Genet 1996;49:28–31.
20. Pober BR, Morris CA. Diagnosis and management of medical problems in adults with Williams-Beuren syndrome. Am J Med Genet Part C 2007;145C:280–290.
21. Viana MM, Frasson M, Leão LL, et al. A new case of keratoconus associated with Williams-Beuren syndrome. Ophthalmic Genetics 2013;34:174–177.
22. Cherniske EM, Carpenter TO, Klaiman C, et al. Multisystem study of 20 older adults with Williams syndrome. Am J Med Genet A 2004;131:255–264.