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Suh, Soh
Le, Alan
Demer, Joseph

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Size of the Oblique Extraocular Muscles and Superior Oblique Muscle Contractility in Brown Syndrome

Soh Youn Suh,[1,2] Alan Le,[1–4] and Joseph L. Demer[1–5]

[1]Department of Ophthalmology, David Geffen Medical School at University of California, Los Angeles, California, United States
[2]Stein Eye Institute, David Geffen Medical School at University of California, Los Angeles, California, United States
[3]Neuroscience Interdepartmental Program, David Geffen Medical School at University of California, Los Angeles, California, United States
[4]Bioengineering Interdepartmental Program, David Geffen Medical School at University of California, Los Angeles, California, United States
[5]Department of Neurology, David Geffen Medical School at University of California, Los Angeles, California, United States

Correspondence: Joseph L. Demer, Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90095-7002, USA;
jld@jsei.ucla.edu.

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Purpose. This study employed magnetic resonance imaging (MRI) to investigate possible size and contractility changes in the superior oblique (SO) muscle, and possible isometric hypertrophy in the inferior oblique (IO) muscle, resulting from abnormal mechanical loading in Brown syndrome (BrS).

Methods. High resolution orbital MRI was obtained in 4 congenital and 11 acquired cases of BrS, and compared with 44 normal subjects. Maximal cross-section areas and posterior partial volumes (PPVs) of the SO were analyzed in central gaze, supraduction, and infraduction for the SO, and in central gaze only for the IO.

Results. In congenital BrS, mean maximum SO cross-sectional areas were 24% and 20% less than normal in affected and unaffected eyes, respectively ($P = 0.0002$). Mean PPV in congenital BrS was also significantly subnormal bilaterally (29% and 34% less in affected and unaffected eyes, respectively, $P = 0.001$). However, SO muscle size and volume were normal in acquired cases. The SO muscle did not relax in supraduction in BrS, although there was normal contractile thickening in infraduction. The IO muscle had normal size bilaterally in BrS.

Conclusions. Congenital BrS may be associated with SO hypoplasia that could reflect hypoinnervation. However, unique isometric loading of oblique extraocular muscles due to restrictive hypotropia in adduction in BrS is generally not associated with changes in muscle bulk or in SO contractility. Unlike skeletal muscles, the bulk and contractility of extraocular muscles can therefore be regarded as independent of isometric exercise history. Restriction to elevation in BrS typically arises in the trochlea–tendon complex.

Keywords: extraocular muscle, magnetic resonance imaging, strabismus

The hallmark of Brown syndrome (BrS) is restrictive limitation to supraduction in adduction. In 1950, Harold Whaley Brown first coined the term "superior oblique tendon sheath syndrome," supposing a short superior oblique (SO) tendon sheath as the cause.[1] In 1975, Parks[2] reported that a restrictive band posterior and inferior to the globe limited elevation in adduction in BrS. In 1982, Helveston[3] suggested fluid accumulation or concretion in the bursa-like space, or vascular distention in the SO tendon sheath, as causes of acquired BrS, impairing SO tendon travel through the trochlea. Subsequent studies have confirmed that pathology generally lies in abnormal SO tendon–trochlea complex,[4,5] although another mechanism involving inferior slip of the lateral rectus pulley has also been identified.[6]

The classical mechanism of BrS provides a unique window into extraocular muscle physiology. Impaired SO tendon travel through the trochlea in BrS prevents the SO muscle from elongating during its innervational relaxation in attempted supraduction in adduction. Consequently, the SO experiences unusual reduction in contractile force without corresponding elongation by its antagonist inferior oblique (IO) muscle. Therefore, the SO experiences isometric relaxation, and the IO experiences isometric contraction, during which it would contract against the unyielding load of the immobile SO tendon "stuck" in the trochlea. While isometric behavior is decidedly unphysiological for extraocular muscles, for skeletal muscles, isometric exercise has been advocated to promote growth. This compensatory hypertrophy can be determined by measuring changes in muscle cross-sectional area, and skeletal muscle hypertrophy is demonstrable in humans after isometric exercise.[7,8] However, the structure and biological behavior of extraocular muscles is so different from skeletal muscles that the behavior of extraocular muscles cannot be extrapolated from skeletal muscles.[9]

Magnetic resonance imaging (MRI) has been widely employed to characterize quantitative morphology and contractility of the extraocular muscles.[10–14] For example, MRI has demonstrated significant hypertrophy of the contralesional superior rectus, and hypercontractility of the contralesional vertical rectus muscles in SO palsy.[12,13] Previous studies have imaged the SO muscle in BrS, demonstrating occasional hypoplasia in congenital cases.[6,15,16] We therefore reasoned

that BrS represents a unique opportunity to determine if extraocular muscles undergo morphologic changes in response to isometric contraction and relaxation; hypertrophy for the IO muscle and hypotrophy for the SO muscle. This study employed MRI to evaluate the size and contractility of the SO, and the size of the IO, in orbits affected by BrS to seek evidence of changes related to abnormal mechanical loading in this disorder.

Methods

This prospective, observational study was conducted at Stein Eye Institute, a single academic medical center at the University of California, Los Angeles (UCLA). Volunteers gave written, informed consent according to a protocol approved by the UCLA Institutional Review Board that conformed to the tenets of the Declaration of Helsinki. This study included 15 cases (4 congenital, 11 acquired) of BrS not previously operated, and 44 age-matched, healthy, orthotropic control subjects. Of 15 cases, 13 had unilateral and 2 had bilateral BrS. The mean age of patients with BrS at 31.5 ± 23.3 years (range, 1.5–69 years) was closely matched to that of the normal subjects at 32.7 ± 18.6 years (range, 19–69 years, $P = 0.25$). There were 3 males and 12 females with BrS, and 18 males and 26 females in the control group.

Healthy control subjects underwent comprehensive eye examinations to verify normal corrected vision, ocular motility, and stereoacuity. Subjects with BrS underwent complete ophthalmic examination, including a Hess screen test where age appropriate, measurement of binocular alignment by alternate prism cover testing in cardinal gazes and head tilt positions, and ocular versions quantified on a 9-point scale, with 0 as a normal, –4 as not passing the midline, and +4 as maximal. The mean central gaze hypotropia in BrS was 6.3 ± 9.5Δ (range, 0–30Δ). The mean underelevation in adduction was –3.4 ± 0.8 (range, –4 to –2). Mean symptom duration was 3.1 ± 6.7 years (range, 1 month–26 years). All subjects with unilateral BrS showed limitation to supraduction in adduction of the involved eye, but normal ductions in the fellow eye. Forced duction testing with forceps was performed under topical or general anesthesia in 13 subjects with BrS, confirming the mechanical restriction to supraduction in all. There was a palpable click at the involved trochlea in two other subjects with BrS.

High-resolution, T1 or T2-weighted MRI was performed in each subject using a 1.5-T Signa Scanner (General Electric, Milwaukee, WI, USA), employing a facemask-mounted, dual-phased surface coil array (Medical Advances, Milwaukee, WI, USA), as described in detail elsewhere.[10,11] Each orbit was imaged during monocular fixation by that eye in central gaze. In selected cases, imaging was repeated in maximum sustainable infraduction and supraduction during fixation by the scanned eye where supraduction was normal, and monocular fixation by the normal eye in supraduction in BrS where the fellow imaged eye could not supraduct. To image the SO muscle, contiguous 2-mm thick quasi-coronal images were obtained perpendicular to the long axis of the orbit in a matrix of 256 × 256 pixels over a 6 or 8 cm field of view, giving 234 to 313 μm resolution. Axial images of 313 to 390 μm resolution were also obtained to view the trochlea and reflected tendon. Quasi-sagittal images parallel to the long axes of each orbit were obtained at 313 μm resolution to image the IO muscle.

Digital MRI images were quantified using the program *ImageJ* (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). The SO muscle was manually outlined in contiguous images posterior to globe–optic nerve junction, and a cross-sectional area was measured using *ImageJ* (Fig. 1). Cross-sectional areas in four contiguous image planes (–4, –5, –6, and –7) 8 to 14 mm posterior to the globe–optic nerve junction were summed and multiplied by the 2-mm slice thickness to form posterior partial volumes (PPVs). Posterior partial volumes of SO in central and vertical eccentric gazes were compared between the eyes in subjects with BrS, and compared with controls. The IO cross section was obtained by outlining it using *ImageJ* in the quasi-sagittal image plane at the center of the inferior rectus muscle (Fig. 2).[17] Vertical eye positions were determined geometrically from the measured globe radius, and positions of the globe–optic nerve junction relative to the centroid of the orbit.[18]

Main outcome measures were quantitative MRI morphometry, ocular ductions, and binocular alignment as measured using prism-cover testing. Statistical analysis included *t*-testing and ANOVA using GraphPad Prism software (GraphPad Software, La Jolla, CA, USA).

Results

SO Size

Mean SO cross-sectional areas were plotted against image planes from –7 to 5 along the anteroposterior extent of the orbit, with plane 0 defined as that containing the globe–optic nerve junction (Fig. 3). In BrS, mean SO cross-sectional area of affected eyes was significantly subnormal in image planes ranging from –6 to –3, and of unaffected eyes were subnormal from image planes –6 to –4 ($P < 0.05$). Cross sections of the SO were normal in both affected and unaffected eyes in acquired BrS. Maximum SO cross-sectional areas in central gaze were 14.0 ± 1.3 mm^2 (mean ± SE) in the affected eye, and 14.9 ± 0.4 mm^2 in the unaffected eye in congenital BrS, which were not significantly different ($P = 0.680$). Both were significantly smaller than those of normal control group at 18.5 ± 0.3 mm^2 ($P = 0.0004$, $P = 0.018$, respectively). In acquired BrS, maximum SO cross-sectional areas were 17.2 ± 0.9 mm^2 in the affected eye, and 17.6 ± 1.2 mm^2 in the unaffected eye, which were not significantly different ($P = 0.786$). Both were similar to those of the normal controls ($P = 0.110$, $P = 0.320$, respectively, Fig. 4). Mean SO PPVs were 79.2 ± 9.2 mm^3 in the affected, and 73.4 ± 5.0 mm^3 in the unaffected eye in congenital BrS, which were not significantly different ($P = 0.666$). Both were significantly less than the normal value of 111.6 ± 2.6 mm^3 ($P = 0.005$, $P = 0.010$, respectively). Mean superior oblique PPV was 97.2 ± 6.7 mm^3 in affected and 103.3 ± 9.6 mm^3 in the unaffected eye in acquired BrS, which were not significantly different ($P = 0.560$). Both were similar to those of normal controls ($P = 0.059$, $P = 0.326$, respectively, Fig. 5).

SO Contractility

Ten affected eyes with BrS and 25 normal control eyes were analyzed to evaluate SO contractility. Congenital and acquired cases of BrS were pooled for analysis of contractility because multipositional MRI was feasible in only three congenital cases, and because findings in congenital cases were qualitatively similar to those of acquired cases. Vertical eye positions during MRI did not differ significantly from normal controls in either eye of subjects with BrS for both supraduction and infraduction ($P = 0.616$, Fig. 6). In normal controls, maximum SO cross-section increased, and the point of maximum cross section area shifted posteriorly during contraction. Conversely, the SO cross-section decreased and the point of maximum cross-

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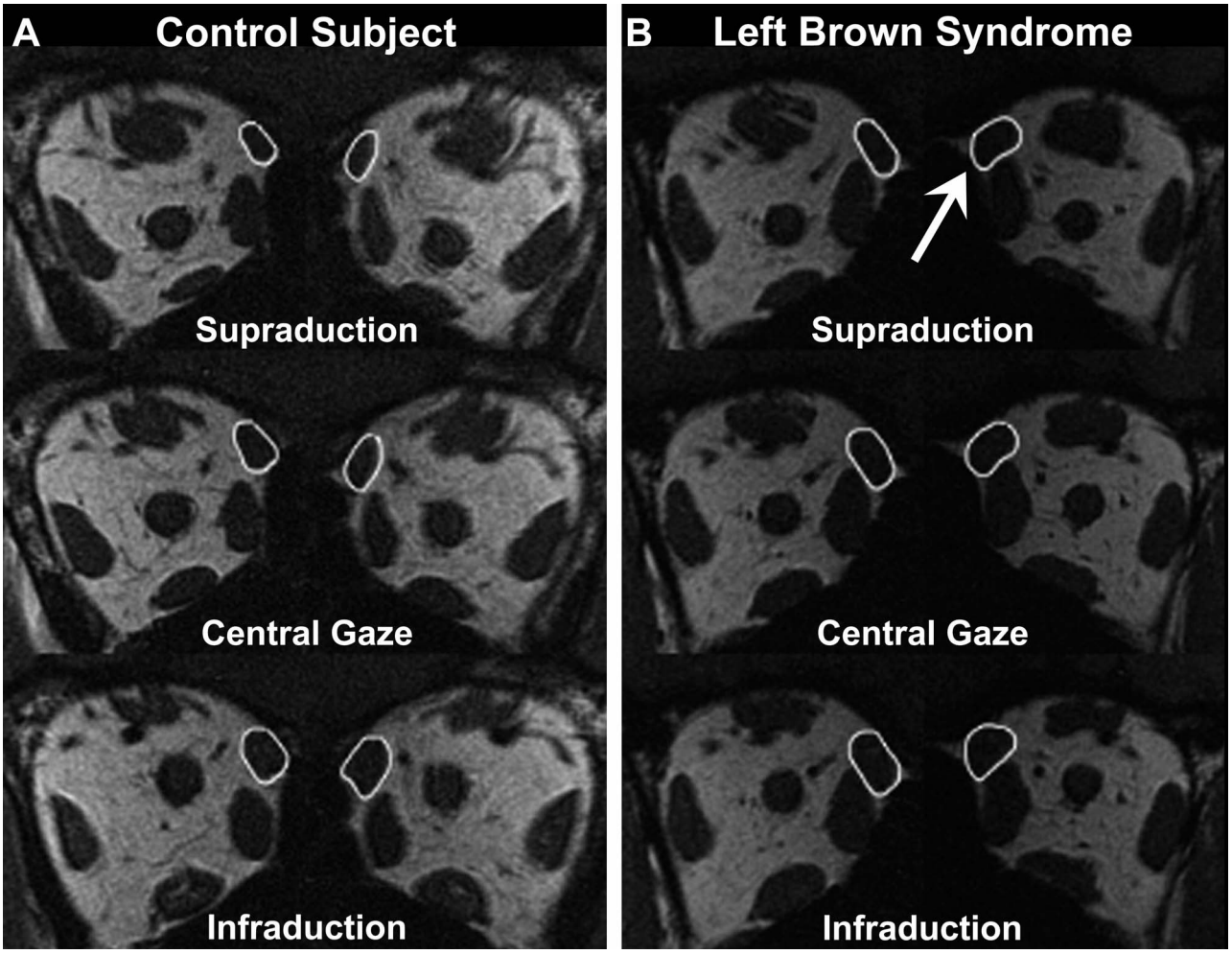

FIGURE 1. Quasi-coronal MRI of orbits in left control subject (**A**) and in BrS (**B**). *Arrow* indicates absence of reduction in left SO cross-section in supraduction.

section area shifted anteriorly during relaxation (Fig. 7A). In BrS, the affected SO did not exhibit reduced cross-section in supraduction, although typical contractile behavior in infraduction was preserved (Fig. 7B). Mean PPVs of the normal control SO was 115.4 ± 5.3 mm^3 in central gaze, decreased to 96.6 ± 4.0 mm^3 in supraduction, and increased to 131.8 ± 5.2 mm^3 in infraduction (ANOVA, $P < 0.0001$). Mean PPVs of the affected SO in BrS was 85.9 ± 6.5 mm^3 in central gaze, decreased to 79.6 ± 8.2 mm^3 in supraduction, and increased to 107.3 ± 9.3 mm^3 in infraduction. The differences were significant between central gaze and infraduction, and infraduction and supraduction ($P = 0.032$, $P = 0.0007$, respectively, Fig. 8). The PPVs of the affected SO did not change significantly from central gaze to supraduction in BrS ($P = 0.384$, Fig. 8). Contractility of the fellow eye in BrS was not systemically investigated to scanning time limitations.

IO Size

Maximum IO cross-sectional areas in central gaze were 15.6 ± 0.6 mm^2 (mean ± SE) in the affected eye, and 15.4 ± 0.8 mm^2 in the unaffected eye in BrS, which were not significantly different ($P = 0.842$). Both were similar to those of normal control group at 14.7 ± 0.3 mm^2 ($P = 0.149$, $P = 0.352$, respectively, Fig. 9).

DISCUSSION

The etiology of BrS has been classically believed to be an abrupt restriction of SO tendon relaxation through the trochlea

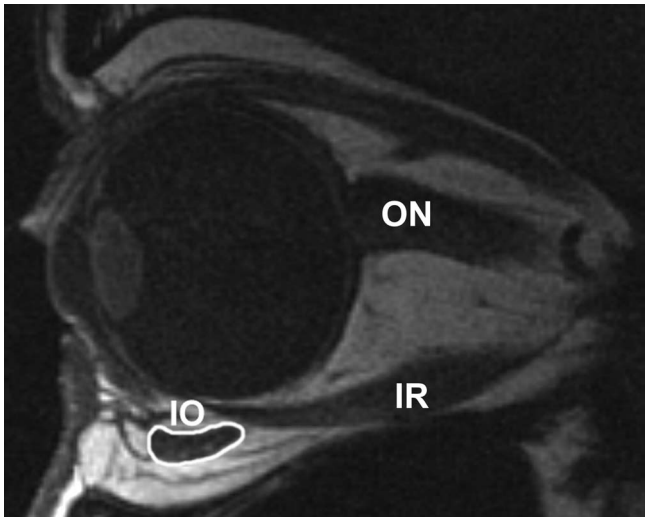

FIGURE 2. Quasi-sagittal MRI of right orbit in a subject with right BrS. IR, inferior rectus muscle; ON, optic nerve.

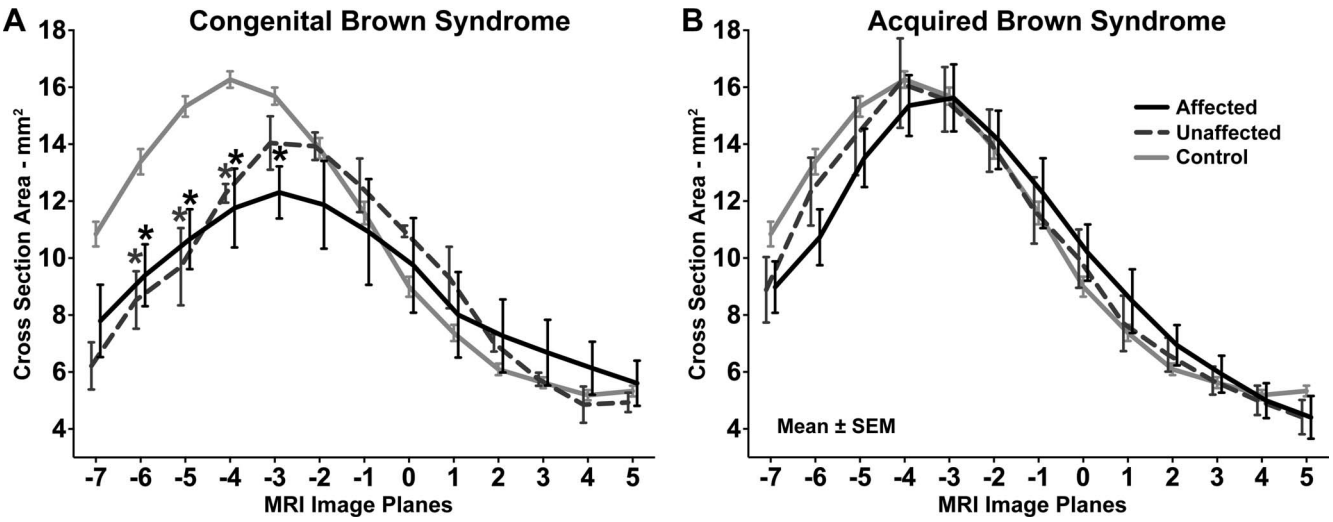

Figure 3. Mean cross-sectional area of the superior oblique muscle in central gaze, measured in 2-mm thickness MRI planes numbered negatively posterior and positively anterior to globe–optic nerve junction (plane 0) in affected and unaffected orbits in BrS and in normal controls. (**A**) Congenital Brown syndrome. (**B**) Acquired Brown syndrome. Significant differences ($P < 0.05$) from normal are indicated by *asterisks*.

in adducted supraduction, violating the nearly universal agonist-antagonist reciprocity otherwise typical of extraocular muscle function. This abnormal condition places the SO belly in the highly unusual situation of isometric relaxation as innervation decreases while its length is unchanged in adducted supraduction. By high-resolution MRI, the present study confirms in BrS that relaxation of the SO muscle is impaired in supraduction, yet SO contraction is preserved in infraduction. In the absence of normal antagonist elongation of the relaxing SO muscle when its tendon sticks in the trochlea during attempted supraduction, its maximum cross-section and PPV remain similar to values in central gaze, rather than decreasing in the manner normally observed. This finding suggests that two morphometric indicators of extraocular muscle contractility, maximum cross-sectional area and PPV, do not change during isometric relaxation as they do during physiologic eye movement when both muscle loading and muscle length change concurrently. The capability of the same SO muscle bellies to exhibit typical contractile increases in maximum cross-section and PPV in infraduction provides reassurance that these muscles remain capable of generating active force. However, the absence of significant differences in size between affected and unaffected SO muscles argues that the unusual loading condition of this situation, isometric relaxation, does not induce a long-term trophic change in SO size in acquired BrS. The long-term SO atrophy that might have been expected on the basis of skeletal muscle response to isometric unloading[19] was not observed in acquired BrS. Significant SO hypoplasia was observed only in congenital BrS, a situation in which additional developmental factors besides isometric unloading may contribute to SO hypoplasia.

Of course, in BrS, when the affected SO undergoes isometric relaxation, its antagonist IO experiences isometric contraction. While isometric exercise is well-known to induce skeletal muscle hypertrophy, the IO ipsilateral to BrS did not increase significantly in cross-section. Consistent with the absence of isometric atrophy in the SO, there was no isometric exercise hypertrophy in the IO in BrS. Thus, the absence of effect of isometric exercise on extraocular muscle size is yet another of the many differences from skeletal muscle behavior.[9]

Previous MRI studies focused on localizing pathologic abnormalities in BrS.[6,15,20] While MRI in one prior congenital case showed no change in SO cross-section during vertical gaze

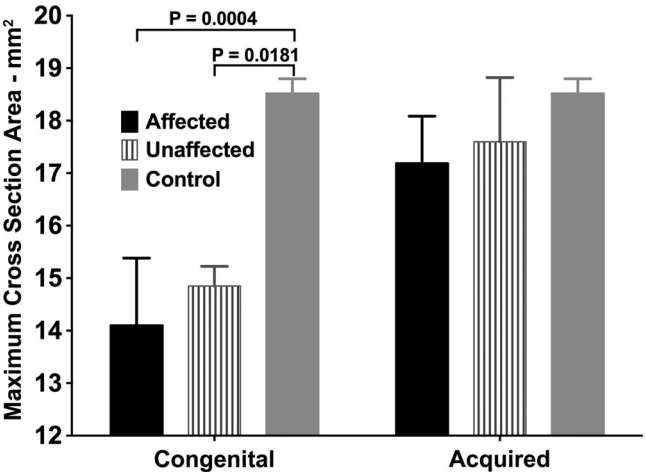

Figure 4. Mean maximum cross-sectional area of the superior oblique muscle in congenital and acquired BrS.

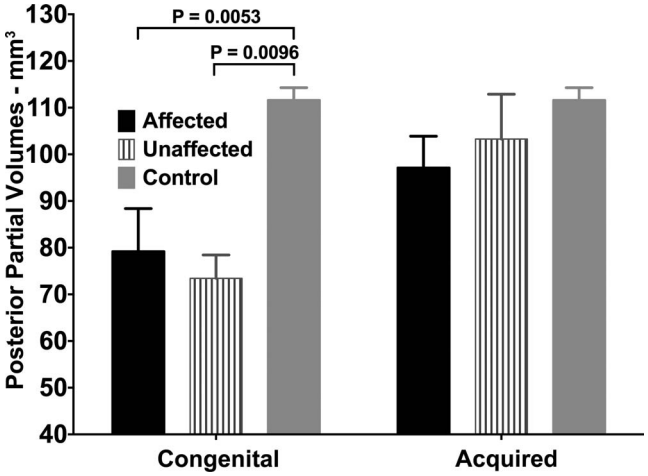

Figure 5. Mean posterior partial volume of the superior oblique muscle in congenital and acquired BrS.

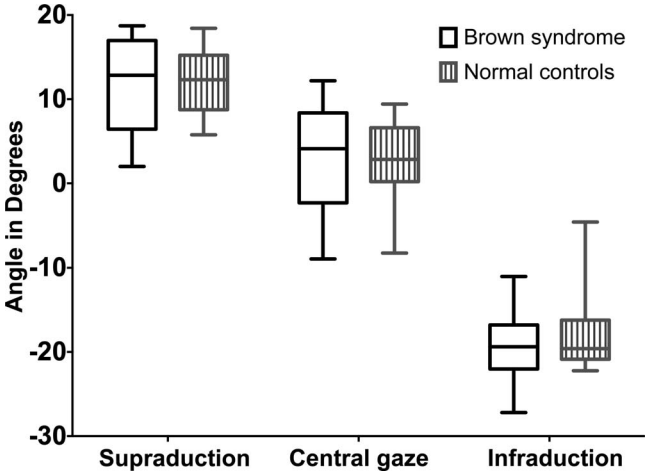

FIGURE 6. Mean vertical eye positions in BrS and normal controls.

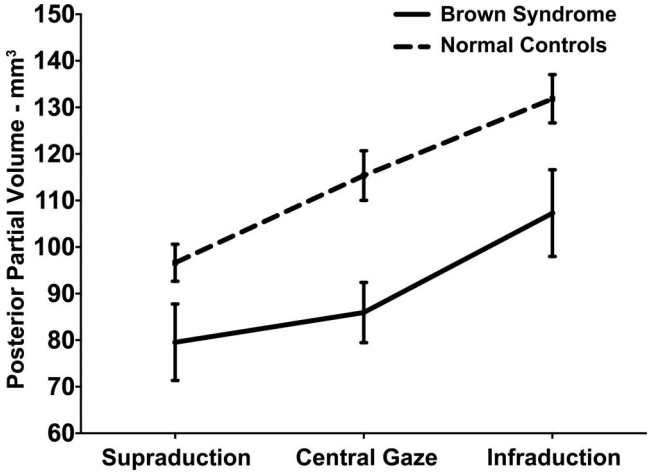

FIGURE 8. Posterior partial volume of the superior oblique muscle in three vertical gaze positions in BrS and normal control subjects. PPV was not significantly different between central gaze and supraduction in BrS.

shift,[16] no prior study in BrS has analyzed the SO through a large anteroposterior extent of the orbit. The current study showed that the SO muscle had significantly subnormal size bilaterally in congenital cases. This might be explained by an asymmetrical developmental abnormality in congenital BrS. Recently, it was proposed that congenital BrS could be regarded as a congenital cranial dysinnervation disorder (CCDD).[16,21,22] Ellis et al.[22] reported three cases of congenital Brown syndrome without clinical SO palsy, who exhibited moderate to severe ipsilateral SO hypoplasia. They suggested that these congenital cases might represent CCDD due to absence of normal trochlear innervation and without misinnervation. They supposed that abnormal trochlear innervation may lead to abnormal SO muscle development, and perhaps secondary changes in the tendon and trochlea that could cause congenital BrS. The association of abnormal SO innervation and SO muscle hypoplasia would be consistent with categorization of some cases of congenital BrS as representing a CCDD. Yet, most cases of congenital SO palsy, which is an unequivocal CCDD, are not associated with BrS.[23–26] Moreover, in a recent MRI study of congenital BrS, Kim and Hwang[27] found qualitatively normal trochlear nerves and SO muscles in nine cases. This implies that innervational and mechanical causes of BrS may be dissociated.

Compartmental SO innervation has recently been recognized, following a pattern reminiscent of the horizontal rectus muscles. The distal trochlear nerve separates into minimally overlapping medial and lateral branches innervating nonoverlapping compartments of muscle fibers. The medial compartment is in continuity with tendon fibers that ultimately insert on the anterior equatorial sclera, with mechanical advantage that accounts for cycloduction. The lateral SO compartment is in continuity with tendon fibers that ultimately insert retroequatorially; with mechanical advantage for infraduction. In BrS impaired, restriction of relaxation of the SO muscle restricts supraduction in adduction. Surgical manipulation of both anterior and posterior SO tendon fibers might create unwanted torsional effect in BrS. Cyclovertical diplopia after SO tenotomy or tenectomy in BrS has been reported.[28] It may be advantageous for SO tendon surgery in BrS target only the posterior fibers to avoid undesired torsion.

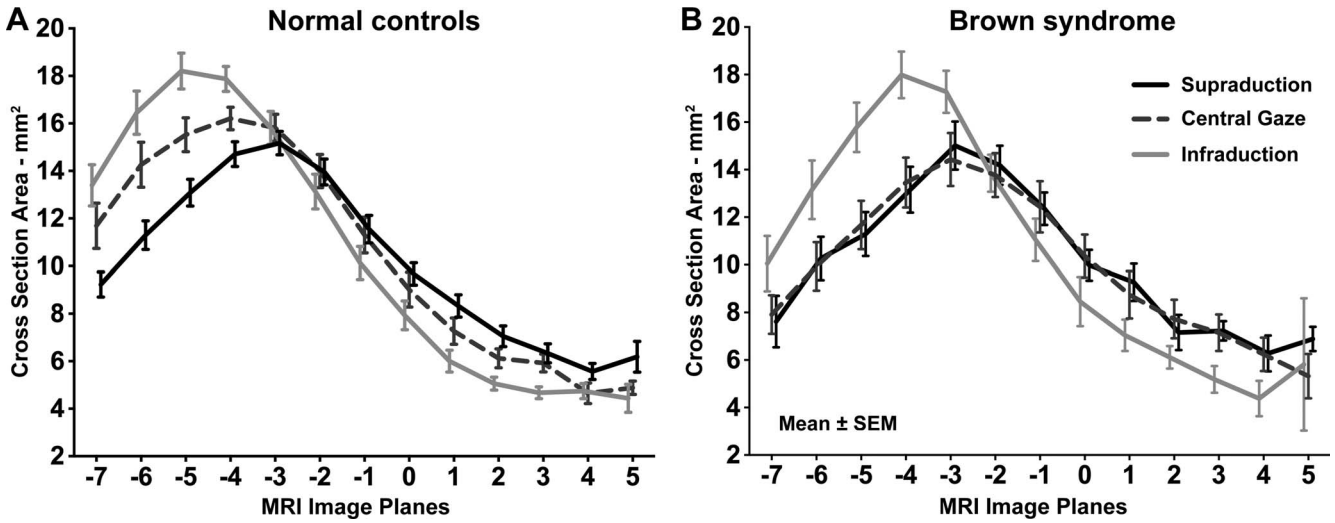

FIGURE 7. Mean cross-sectional area of the SO muscle in three vertical gazes in Brown syndrome (BrS) and normal control subjects. Note absence of change between central gaze and supraduction in BrS. (**A**) Normal controls. (**B**) BrS.

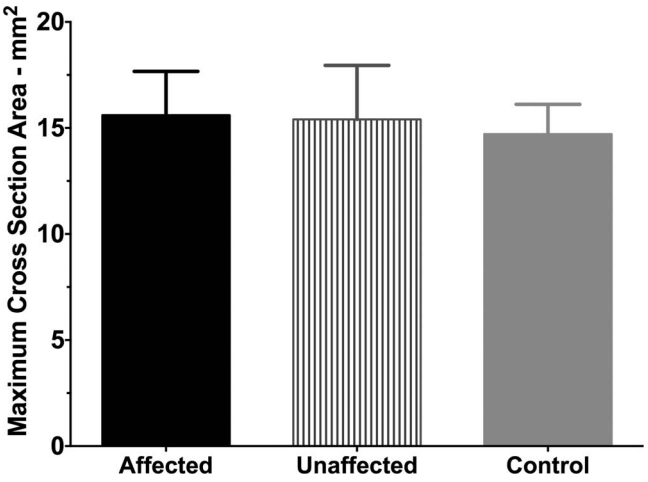

FIGURE 9. Maximum cross-sectional area of the inferior oblique muscle in Brown syndrome.

The present study confirms that it is not the SO muscle belly that limits supraduction in adduction in BrS, but rather the interaction of the SO tendon with the trochlea. Surgical procedures altering the primary pathology of the SO tendon–trochlea complex would ideally be considered for treatment. Trochlear surgery for overdepression in adduction was first introduced in 1940s, but was not performed in BrS.[29] In 1995, Mombaerts et al.[30] described trochlear luxation for treatment of BrS. Recently, trochlear reconstruction and surgical removal of adhesions around the SO tendon–trochlea complex has been described.[31]

This study demonstrates that the SO muscle has subnormal size in congenital BrS but has normal size in acquired BrS. The finding that SO relaxation is impaired by the restricted travel of the SO tendon through the trochlea confirms the SO tendon–trochlear complex as the pathophysiologically ideal target to correct limited supraduction in adduction. Absence of trophic changes in the ipsilesional SO and IO despite isometric loading in BrS illustrate a fundamental physiologic difference between skeletal and extraocular muscles, with a remarkable dissociation between size and loading in the latter.

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