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Synergistic divergence: a distinct ocular motility dysinnervation pattern

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Abstract

Purpose—To summarize the clinical, neuroradiologic, and genetic observations in a group of patients with unilateral synergistic divergence (SD).

Methods—Five unrelated patients with unilateral SD underwent ophthalmologic and orthoptic examinations; three of them also had magnetic resonance imaging of the brain and orbits. Three patients underwent genetic evaluation of genes known to affect ocular motility (*KIF21A*, *PHOX2A*, *HOXA1*, and *ROBO3*).

Results—Patients did not meet clinical criteria for CFEOM types 1, 2, or 3. Each patient had severe adduction weakness on the affected side and a large angle exotropia in primary gaze that increased on attempted contralateral gaze because of anomalous abduction. Magnetic resonance imaging revealed a much smaller medial rectus muscle in the involved SD orbit. Oculomotor cranial nerves were present in the one patient imaged appropriately. Genetic sequencing in three patients revealed no mutations in *KIF21A*, *PHOX2A*, *HOXA1*, or *ROBO3*.

Conclusions—SD should be classified as a distinct congenital ocular motility pattern within congenital cranial dysinnervation disorders. It is possibly caused by denervation of the medial rectus with dysinnervation of the ipsilateral lateral rectus by the oculomotor nerve precipitated by genetic abnormalities (some currently identified) or by local environmental, teratogenic, or epigenetic disturbances.

Introduction

Synergistic divergence (SD) is a congenital ocular motility pattern characterized by paradoxical abduction during attempted horizontal gaze to the contralateral side.¹ This rare condition is generally unilateral and is always associated with limited adduction of the affected eye. The pathophysiology of anomalous abduction remains unclear but has been variously attributed to mechanical factors, anomalous innervation of the ipsilateral medial and lateral recti muscles,^{2, 3} and even anomalous cross innervation between the two lateral recti.⁴ SD is usually an isolated ocular motility abnormality, but it has been described several times in conjunction with ocular motility phenotypes consistent with congenital fibrosis of the extraocular muscles type 1 (CFEOM1)⁵ and type 3 (CFEOM3).⁶

This report summarizes clinical, radiologic, and genetic observations in a group of patients with unilateral SD.

Methods

Five unrelated patients of Middle Eastern ethnicity had complete orthoptic and ophthalmologic examinations, including dilated fundoscopy. Ocular motility was assessed visually and by videotaping. Fusion was measured using the Worth 4 Dot Test and the Lang stereo test.

Standard brain MR pulse sequences were acquired in one patient using a 1.5 Tesla GE Signa scanner (GE Medical Systems, Waukesha, WI) and in two patients using a 3.0 Tesla Siemens Magnetom Allegra scanner (Siemens Medical Systems, Germany), including sagittal T1-weighted spin echo, coronal fluid-attenuated inversion recovery, axial dual echo, and axial proton density inversion recovery sequences in all patients and axial 3D FT constructive interference in steady-state (CISS) of the brainstem in one patient. One patient had brain computerized tomography performed on a Siemens Sensation 4 scanner (Siemens Medical Systems, Germany).

Five ml of peripheral blood was collected in EDTA tubes from three patients and high molecular weight DNA was extracted using the Puregene blood kit (Qiagen, Germany), quantified spectrophotometrically, and stored at –20 degrees C in aliquots until required. *PHOX2A* (MIM *602753),⁷ *HOXA1* (MIM *142955),⁸ and *KIF21A* (MIM *608283)⁹ coding exons and exon-intron boundaries were amplified using polymerase chain reactions (PCR) with Hotstar Taq DNA polymerase (Qiagen, Germany). Two patients also had *ROBO3* (MIM *608630)¹⁰ sequenced. All resulting amplicons for *PHOX2A*, *HOXA1*, and *ROBO3*, and the amplicons for *KIF21A* exons 8, 20 and 21 were direct sequenced on an ABI 3730 Sequence Analyzer (Applied Biosystems, Foster City, CA). The remaining *KIF21A* amplicons were analyzed by denaturing high-performance liquid chromatography (DHPLC, Transgenomic, Inc., Omaha, NE). All screening conditions were as previously published, and primers are available on request. Study protocol adhered to the tenets of the Declaration of Helsinki, and patients signed consent forms approved by the King Khaled Eye Specialist Hospital, Riyadh, or the Children's Hospital Boston.

Results

Birth, general medical history, and family history were unremarkable, although two patients were from consanguineous families (a typical prevalence in the Middle East). Figure 1 illustrates the eye movements of Patients 1, 2, and 3, while the Table presents clinical details. All patients were male, and all had unilateral SD with the right eye involved in four. No family member of Patients 1–4 reported an ocular motility, ophthalmologic, or neurologic abnormality. A brother and sister of Patient 5 had congenital ptosis.

Ocular motility patterns did not meet clinical criteria for CFEOM1,¹¹ CFEOM2,¹² CFEOM3,⁶ horizontal gaze palsy and progressive scoliosis,¹³ or the *HOXA1* clinical spectrum.¹⁴ All patients had a large angle exotropia with the SD eye fixed in an abducted position and unable to adduct sufficiently to reach the midline. On attempted gaze contralateral to the SD eye, the SD eye of each patient abducted incompletely rather than adducting so that both eyes abducted simultaneously. Ipsilateral abduction of the SD eye was also incomplete in all patients. No patient had globe retraction of the SD eye during horizontal gaze or anomalous lid movement on either side with ocular or jaw movement. Additional SD eye motility anomalies included primary position hypotropia which increased during attempted adduction (i.e., coincident with anomalous abduction; Patients 2 and 3); mild elevation and depression deficiency (Patient 4); and a mild elevation deficiency only (Patient 2).

Two patients had Duane retraction syndrome (DRS) in the contralateral eye. Patient 1 had a DRS type 3 with characteristic marked limitation of abduction and adduction of the left eye associated with marked lid fissure narrowing and globe retraction on right gaze. He also had reduced hearing bilaterally. Patient 5 had DRS type 1 on the left with absent abduction, normal adduction, and globe retraction with narrowing of the palpebral fissure during attempted right gaze. All five patients preferred fixation with the non-SD eye, and amblyopia was present in the SD eye of three patients (Patients 1, 4, and 5). Fixation was exclusively monocular in four patients, while Patient 2 adopted an anomalous head position with face turn left in order to obtain fusion documented by Worth 4-Dot Test responses at near and distance and measurable stereopsis on the Lang stereo test. However, this marked head position was too uncomfortable to maintain for prolonged periods, and he would typically revert to fixing monocularly with the non-SD eye.

Only Patient 2 had a surgical correction to reduce his exotropia and eliminate the anomalous divergence movement. Right lateral rectus extripation eliminated the anomalous divergence movement; however, a large exotropia persisted. Three months later he underwent vertical recti transpositions to the medial rectus, at which time the medial rectus muscle was found to be thin and fibrotic.

Patients 1–3 had brain imaging performed. Orbits, skull base, brainstem, and supratentorial brain appeared normal. Figure 2 shows images of Patient 1, documenting a small right medial rectus (2A and 2B) and the presence of oculomotor nerves (2C). The maximum cross-section size of the right medial rectus was approximately 30% of that on the left in all three imaged patients, while other extraocular muscles appeared symmetric in size.

Three subjects had genetic screening for known CCDD genes. *KIF21A*, *PHOX2A*, and *HOXA1* sequencing in Patients 2, 3, and 5 revealed no mutations. *ROBO3* sequencing in Patient 2 and 5 also showed no mutations.

Discussion

We describe five unrelated patients of Middle Eastern ethnicity with unilateral synergistic divergence, an unusual congenital ocular motility pattern consisting of an exotropia due to unilateral absent adduction and bilateral abduction during attempted gaze contralateral to the affected eye.¹ Two patients had DRS contralaterally, and three others had mild vertical motility abnormalities in the SD eye. A small medial rectus muscle was observed in the SD eye of patients who underwent brain imaging. We did not find a mutation in any gene currently identified to cause a congenital ocular motility abnormality.

Patients reported previously 5 and all three patients with brain imaging reported here had small medial recti on the affected side. This might be due to maldevelopment of the medial

rectus muscle, and surgical observation of our Patient 2 and others 1, 15 noted fibrosis and/or hypoplasia of the medial and sometimes the lateral rectus muscles. However, hypoplasia of the affected medial rectus alone would not explain abduction of the affected eye on attempted contralateral gaze.

Recently, certain congenital ocular motility disorders formerly thought due to congenital fibrosis of the extraocular muscles have been reclassified as congenital cranial dysinnervation disorders (CCDDs).¹⁶ These disorders result from the congenital absence or misdirection of specific brainstem lower motor neurons, leading to the loss of correct innervation of certain extraocular and/or cranial muscles, often with subsequent anomalous innervation (dysinnervation) by other nerves.⁷⁻⁹

SD has certain similarities to DRS, the most common CCDD ocular motility pattern. Both SD and DRS affect predominantly horizontal ocular muscles, they both occur unilaterally or bilaterally,¹⁷ and they sometimes coexist.¹⁸ However, the SD clinical phenotype differs from DRS in a number of ways. It involves a different motility pattern from all three DRS types; the muscle most involved is the medial rectus rather than the lateral rectus; and it does not include the DRS clinical hallmarks of globe retraction and lid fissure narrowing. DRS is more common in females for unclear reasons,¹⁷ while SD is more common in males in currently reported patients.¹⁹⁻²²

A likely scenario is that a developmental anomaly in SD prevents the inferior branch of the oculomotor nerve from correctly innervating the medial rectus. The presence of synergistic divergence of the affected globe suggests that oculomotor fibers that should innervate the medial rectus actually innervate the lateral rectus, causing anomalous abduction on attempted contralateral gaze. Medial rectus denervation would explain a small medial rectus and absence of adduction on the affected side, and electromyographic studies in SD have documented reduced or absent firing in the medial rectus compatible with denervation.¹ One of our patients underwent extirpation of the lateral rectus in the SD eye but that eye remained exotropic with no apparent adduction, implying complete denervation of the medial rectus.

SD is sometimes associated with other evidence of miswiring such as Marcus Gunn jaw winking^{20, 23} and anomalous innervation of the medial rectus by the motor branch of the trigeminal nerve.¹⁹ In fact, SD has been reported in patients with CFEOM1,⁵ a genetic abnormality that typically causes widespread extraocular muscle dysinnervation,²⁴ and another previously reported patient with eye movements characteristic of SD had linkage to the CFEOM3 locus.⁶ Two of our patients had contralateral DRS, and three others had mild anomalous vertical eye movements. These observations indicate that miswiring extends beyond the horizontal rectus muscles in the SD eye in all of our patients. The negative genetic results reported here prove that SD is not exclusively associated with currently identified CCDD genes but also may be due to currently unrecognized genetic abnormalities or to local environmental, teratogenic, or epigenetic disturbances during development.

SD deserves recognition as a distinct ocular motility pattern of CCDD, comparable to DRS but much less common. It is possibly caused by congenital denervation of the medial rectus with dysinnervation of the ipsilateral lateral rectus, resulting in the characteristic anomalous abduction bilaterally on attempted contralateral gaze. Future studies may elucidate the genetic and/or teratogenic factors during development that cause this CN misdirection pattern.

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Figure 1. Montage of ocular alignment and motility

Horizontal ocular motility montage of Patients 1 (A, B, C), 2 (D, E, F), and 3 (G, H, I).

Primary position (B, E, H) included a large angle right exotropia in each patient. Right gaze (A, D, G) resulted in good but not complete abduction of the right eye in each patient. Right exotropia increased on left gaze (C, F, I) in each patient because of an abducting movement of the right eye, i.e. synergistic divergence. Patient 1 also had a motility pattern in the left eye compatible with DRS Type 3. Patients 2 and 3 had a small right hypotropia in primary position that was exaggerated by a down shoot of that eye on attempted left gaze. None of these 3 patients had globe retraction on the right.

Figure 2. Montage of brain imaging

Images of Patient 1. (A) Axial CT image of orbit showing smaller medial rectus muscle on right. Right optic nerve is marked by “*” and medial recti by arrows. (B) Coronal T2W MRI image of orbits again showing smaller medial rectus muscle on right. Medial recti marked by arrows. (C) Axial CISS MRI image showing normal-appearing oculomotor nerves marked by arrows bilaterally. Images did not adequately demonstrate the presence or absence of the abducens nerves.

Table

Clinical details

Patient	Age (yrs)	SD eye	Fellow eye	Ocular Alignment	Horizontal Ocular Motility*				Vertical Ocular Motility SD eye [‡]
					SD eye		Fellow eye		
					ABD	ADD	ABD	ADD	
1	2	Right	DRS Type 3	XT 85	75%	0% [‡]	25%	25%	Full
2	9	Right	Normal	XT 55 RHypoT 8 with AHP; X 2	75%	0% [‡]	100%	100%	Mild elevation deficiency; Down shoot during attempted adduction
3	1	Right	Normal	XT 60 RHypoT 10	85%	0% [‡]	100%	100%	Full; Down shoot during attempted adduction
4	5	Left	Normal	XT 70	90%	0% [‡]	100%	100%	Mild elevation and depression deficiency
5	3	Right	DRS Type 1	XT 70	75%	0% [‡]	0% [§]	100%	Full

Age = age at first exam; SD eye = eye having synergistic divergence; ABD = abduction; ADD = adduction; DRS = Duane retraction syndrome; XT = exotropia; X = exophoria; RHypoT = Right Hypotropia.

* Duction movement scored as a percentage of normal excursion where 100% = full movement and 0% = no movement into field of action.

[†] Contralateral (non-SD eye) had full vertical ocular motility in all patients.

[‡] Eye unable to reach midline (i.e. straight ahead position) and remains in an abducted position.

[§] Eye unable to reach midline (i.e. straight ahead position) and remains in an adducted position