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Magnetic Resonance Imaging of Innervational And Extraocular Muscle Abnormalities In Duane-Radial Ray Syndrome

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Abstract

Purpose—We employed magnetic resonance imaging (MRI) to study extraocular muscles (EOMs) and nerves in Duane-radial ray (Okhihiro) syndrome (DRRS) due to mutations in the transcription factor *SALL4*.

Methods—We examined four male and two female affected members of a pedigree previously reported to co-segregate DRRS and a heterozygous *SALL4* mutation. Coronal T1 weighted MRI of the orbits and heavily T2 weighted images in the plane of the cranial nerves were obtained in four subjects. MRI findings were correlated with motility examinations, and published norms obtained using identical technique.

Results—Five of the six subjects with DRRS had radial ray abnormalities including thumb, radial artery, radial bone, and pectoral muscle hypoplasia. Three had bi- and three unilateral ocular involvement. Seven eyes had limitation of both ab- and adduction, while two had limitation only of abduction. Most affected eyes had lid fissure narrowing and retraction in adduction. Intraorbital and intracranial abducens nerves (CN6) were small to absent, particularly ipsilateral to abduction deficiency. All cases undergoing MRI had normal intracranial oculomotor nerves (CN3). Optic nerve (ON) cross section was similar to normal. EOMs and pulleys were structurally normal in most cases. In some affected orbits, a branch of CN3 closely approximated and presumably innervated the LR.

Conclusions—DRRS has a Duane syndrome phenotype, with a variable and asymmetric endophenotype including marked CN6 hypoplasia and probable innervation or co-innervation of the LR by CN3. This endophenotype is more limited than reported in DURS2-linked Duane syndrome and CFEOM1, which are clinically similar congenital dysinnervation disorders that feature, in addition, CN3 hypoplasia and more widespread EOM abnormalities.

Keywords

Duane syndrome; extra-ocular muscle; cranial nerve; optic nerve; pulley

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Proprietary Interest: None.

Duane retraction syndrome (DRS) is characterized by congenital horizontal duction deficit, narrowing of the palpebral fissure on adduction, and globe retraction with occasional upshoot or downshoot in adduction¹. Innervation of the lateral rectus (LR) by the abducens nerve (CN6) is deficient in both DRS and CN6 palsy, although unlike CN6 palsy, the eyes in central gaze are frequently aligned in DRS². This evidence for contractile tonus in the LR suggests that the involved LR is either solely, or co-innervated, by a branch of the oculomotor nerve (CN3). Early electrophysiological studies of sporadic DRS suggested absence of normal CN6 innervation to the LR muscle as the cause of DRS, with paradoxical LR innervation in adduction^{3,4}. Absence of the CN6 nerve and motor neurons with LR innervation by an aberrant CN3 branch has been confirmed by autopsy in one sporadic unilateral⁵ and another sporadic bilateral DRS case⁶. Parsa *et al.* first used magnetic resonance imaging (MRI) to demonstrate absence of the subarachnoid CN6 in sporadic DRS⁷, a finding confirmed in some but not all sporadic and familial cases^{8–11}.

While many DRS cases appear sporadic, the less common inherited forms can provide molecular genetic and phenotypic insights. Isolated DRS can segregate as a dominant trait in large pedigrees and has been linked to chromosome 2 (DURS2 locus)^{12–14}. High-resolution MRI in affected members of DURS2-linked DRS pedigrees (referred to as “DURS2” below) revealed small to undetectable CN6s, as well as providing direct evidence of LR innervation by CN3, and CN3 and the optic nerve abnormalities¹¹. These MRI studies indicate that the endophenotype, the internal phenotype of the structure and function of EOMs, may be complex and variable, not reflective of seemingly similar external findings in subjects with DRS. The DURS2 gene has not yet been identified.

The present study was performed to characterize the endophenotype in a family with Duane radial ray syndrome (DRRS), (also known as Okiihiro syndrome, OMIM 607323). DRRS is the dominant association of uni- or bilateral DRS with uni- or bilateral dysplasia of the radial bone, artery, and thumb, and can result from heterozygous mutations in *SALL4*, a zinc finger transcription factor^{15,16}. The developmental expression profile and functional role of *SALL4* in normal and abnormal ocular motor development have not yet been elucidated, and *SALL4* mutations have not been identified in individuals with isolated sporadic DRS¹⁷.

METHODS

Subjects and Clinical Examination

Six affected members of a single pedigree previously reported to harbor a *SALL4* single base-pair deletion, 1904delT (Pedigree V¹⁵), agreed to undergo clinical examinations and MRI after giving written informed consent to a protocol conforming to the Declaration of Helsinki and approved by relevant institutional review boards. Subjects underwent examination of corrected visual acuity, ocular motility, eyelid structure and function, binocular alignment, anterior segment anatomy, and ophthalmoscopy. Ophthalmic histories were obtained, with corroboration of previous ocular surgeries from operative records where possible.

Magnetic Resonance Imaging was performed with a 1.5 T General Electric Signa scanner (Milwaukee, WI) in four subjects. Subject 1 is a child who was unable to undergo MRI due to metallic dental braces, and Subject 4 had a claustrophobic reaction before MRI could be conducted. Orbital imaging was performed as described elsewhere in detail^{18–22}. Imaging posterior to the orbital apex in some subjects was performed using the standard head coil. When surface coils were used, images of 2 mm thickness in a matrix of 256 × 256 were obtained over a field of view of 6 – 8 cm for a resolution in plane of 234 – 312 μm. Imaging of subarachnoid cranial nerves was performed in 1 mm thickness image planes using the heavily T2 weighted FIESTA sequence^{23,24}. In plane resolution was 195 μm over a 10 cm field of view (matrix 512 × 512) with 10 excitations.

Digital MRI images were quantified using the programs NIH *Image* 1.59 and *ImageJ* 1.33 μ (W. Rasband, National Institutes of Health). In coronal planes, each rectus EOM was described by the “area centroid” using methods previously described²⁵. Cross sectional areas were determined using *ImageJ*, which due to a difference in perimeter treatment produces different area values than NIH *Image*. Centroid determinations do not differ between NIH *Image* and *ImageJ*. The globe center was determined²⁰. Coronal plane pulley locations were determined from the EOM centroids at published anteroposterior positions²⁰. Inferior oblique (IO) muscles were analyzed using outlined cross sections in quasi-sagittal images²⁶. Optic nerve cross sections were analyzed in the first image plane immediately posterior to the globe²⁷.

We computed rectus EOM volumes by summing the cross sections for each EOM in the image plane containing the junction of the globe and optic nerve, and the next five contiguous image planes posterior to this plane, then multiplying by the image plane thickness of 2 mm. While this approach fails to account for EOM volume deep to the image planes collected, the technique was identical to that used for published data in control subjects and subjects with CFEOM1²⁴, and DURS2¹¹. This technique avoids the confounding problem of defining the borders of highly dysplastic deep portions of EOMs.

RESULTS

Clinical Findings in DRRS

General subject characteristics are summarized in Table 1. Mean corrected visual acuity was identical in left and right eyes of affected subjects (Table 1), and averaged -0.02 logMAR (20/20⁺ Snellen). The maximum interocular acuity difference observed was 0.45 logMAR, found in Subject 6, indicating minimal to no amblyopia.

Subjects exhibited a variable and often asymmetrical pattern of abnormalities of the radial bone, radial artery and thumb, as detailed in Fig 1 and Table 1. Subject 2 had, in addition, hypoplasia of the left pectoral musculature.

Subjects 2, 3, and 6 exhibited unilateral ocular motility abnormalities. Subject 1 exhibited asymmetrical and subjects 4 and 5 exhibited symmetrical bilateral DRS. Posterior globe displacement, termed retraction, was evident on attempted adduction of all affected eyes except Subjects 3 and 4, where this finding could not be ascertained with certainty. Horizontal saccades were slowed in the direction of limited duction in affected eyes, and appeared normal in unaffected directions and unaffected eyes. Vertical saccades were examined in all subjects except Subject 2, in whom this was omitted due to time considerations. Vertical saccades were normal in all examined subjects except for Subject 4, who was unable to make vertical saccades, but had a normal range of vertical slow phases during vestibular stimulation by the doll's head maneuver. Subject 4 had almost complete horizontal ophthalmoplegia even to the horizontal doll's head maneuver, but had some convergence. No subject exhibited blepharoptosis. Subjects 1 and 5 had previously undergone surgeries for strabismus correction prior to the study. The remaining subjects had not undergone prior ocular surgery.

The common clinical classification by Huber of DRS consists of three groups: type 1, with limitation of abduction only; type 2, with limitation of adduction only; and type 3, with limitation of both ab- and adduction^{3,28}. This classification is interpreted here with respect to duction along the horizontal meridian, since the limitation in several subjects varied markedly with vertical eye position. As noted in Table 1, five right and two left eyes were classified as DRS type 3, while two left eyes exhibited DRS type 1. Subject 1 exhibited DRS type 3 on the right, and type 1 on the left, with the left eye additionally exhibiting limited supraduction. Subjects 4 and 5 had bilateral type 3.

As indicated in Table 1, three affected subjects exhibited esotropia in central gaze, and one exhibited exotropia. The strabismus was unaltered (concomitant) during vertical gaze changes in Subjects 2 and 3 only, but varied with vertical gaze in Subjects 1 and 5. Subject 1 had incomitant horizontal strabismus evocative of the letter “A” or Greek letter “lambda” because the eyes were in a more divergent position in down gaze than up gaze. Subject 5 had exotropia that increased in upward gaze.

Orbital Imaging Findings in DRRS

Structural abnormalities of EOMS were not severe or common among subjects with DRRS. Only Subject 5 had splitting of the deep portion of the right LR, and hypoplasia of the deep portion of the left LR (Fig. 3). The EOMs were structurally normal in the remaining subjects who underwent MRI.

Quantitative Analysis of Rectus EOMs

Even despite prior strabismus surgery, orbital MRI reasonably reflects the sizes and positions of EOM bellies since surgery is largely confined to the region of the insertional tendons¹¹. Mean volumes of each of the four rectus EOMs in the six contiguous image planes including and posterior to the junction of the globe and optic nerve were not significantly different from normal when both orbits of each subject were included ($P > 0.05$, Table 2). The volume measurement did not, however, incorporate rectus EOMs in their most apical portions. Mean rectus EOM volumes in DRRS were also not significantly different from those previously reported in DURS2¹¹. A similar analysis limited to orbits affected by DRS also showed no significant differences from normal.

Quantitative Analysis of Oblique EOMs

Previously reported control IO volume averages 301 ± 11 microliters ($N = 55$)¹¹. Quasi-sagittal imaging was performed in Subjects 2, 3, and 6. Considering both eyes of these subjects, mean IO volume was 251 ± 25 microliters, not significantly different from normal. However, Subjects 2 and 3 had subnormal IO volumes of 160 – 186 microliters, offset by above normal volumes in Subject 6 of 353 and 450 microliters.

For comparability to the published literature, SO size was assessed by maximal cross section in quasi-coronal image planes. Considering both eyes of the 10 normal subjects previously reported¹¹, mean maximal SO cross section was 22.0 ± 0.9 (SEM) mm². Averaging over both eyes of the four subjects with DRRS who were imaged, mean maximal SO cross section was not significantly different from normal at 24.5 ± 0.9 mm².

Rectus Muscle Paths

The EOMs pass through their connective tissue pulleys, so that the anterior locations of these paths indicate the respective pulley locations in the coronal plane²². Since subjects with DRRS were typically unable to achieve eccentric gaze positions, no inflections in rectus EOM paths were present to identify the anteroposterior coordinates of the rectus pulleys. It therefore was assumed the rectus pulley anteroposterior coordinates are the same as those known for normal subjects²². This was considered reasonable, since variations in anteroposterior coordinates would minimally influence horizontal and vertical pulley coordinates. The coordinates of rectus pulleys in DRRS did not differ significantly from normal ($P > 0.005$), except for 3 – 4 mm lateral displacement of the superior rectus (SR) that was due entirely to Subjects 2 and 5, who were the only subjects to exhibit the displacement.

Imaging of Intraorbital Motor Nerves

It was possible to examine in the deep orbit the motor nerves to the EOMs in image planes of 1.5–2 mm thickness, and field of view 6–8 cm. Normal intraorbital motor nerves to individual EOMs are represented by one or at most a few pixels in the coronal image planes employed here; images of intraorbital motor nerves are insufficiently precise for quantitative analysis of motor nerve size. However, qualitative impressions were consistently obtained and are illustrated here. Assessments were confirmed by evaluation of multiple contiguous MRI planes to trace the paths of presumed nerves to their target EOMs.

The intraorbital CN6 was absent or below detection in the right orbit of Subjects 2 and 6, who both exhibited right DRS type 3. The intraorbital CN6 was absent or below detection in the left orbit of Subject 3, who exhibited left DRS type 1. Subject 5 had an identifiable CN6 in each orbit and exhibited DRS type 3. In the right orbit of Subjects 5 and 6, and in the left orbit of Subject 3, a branch of CN3 was in close contact with the inferior belly of the LR (Fig. 3). The intimate contact of the inferior division of CN3 with the LR suggested that the CN3 branch entered the EOM, although the limited resolution of MRI precludes confirmation of actual innervation at the level of EOM fibers. The MR and IR were innervated by CN3 branches in all orbits imaged, although in Subjects 2 and 3 these motor nerves appeared subnormal in size.

Imaging of Intracranial Motor Nerves

Heavily T2-weighted imaging of the skull base region was conducted in 1 mm thickness slices at 195 μ m resolution in the plane of the optic chiasm and major cranial nerves to the orbit. This technique has just sufficient resolution to consistently demonstrate normal subarachnoid CN6s, while it consistently demonstrates the larger CN3s of normal subjects (Fig. 6)^{11,24}.

The right subarachnoid CN6 was not demonstrable in Subjects 2 and 6. In Subject 3 the left subarachnoid CN6 appeared smaller than the right, while in Subject 5 the right CN6 appeared smaller than the left, and the left appeared dysplastic. The CN3 was present in all subjects with DRRS imaged. Averaging bilaterally, mean $\pm$ SEM CN3 width was 1.91 ± 0.13 mm in affected subjects, not significantly different from the width of 2.10 ± 0.07 mm for normal subjects²⁹.

Optic Nerve

Since ON cross section normally decreases from anterior to posterior in the orbit due to the reduction of connective tissues surrounding the axon bundles²⁷, ON cross sections were analyzed at the 2 mm thick image plane thickness closest to the globe-optic nerve junction. Mean ($\pm$ SEM) cross section of the optic nerve in 8 orbits with DRRS was 8.90 ± 0.44 mm², not significantly different from normal. The ON also appeared ophthalmoscopically normal in all subjects.

DISCUSSION

Definition of the DRRS Endophenotype

As this and previous published pedigrees demonstrate, different affected family members harboring the same *SALL4* mutation can exhibit unilateral or bilateral DRS of type 1 or 3 [Al-Baradie, 2002 #6341]. This suggests that there are additional genetic and/or environmental factors that modulate the phenotype in DRRS.

MR imaging in the four DRRS family members reveals a spectrum of CN6 endophenotypes: undetectable both intracranially and intraorbitally on the affected side in Subjects 2 and 6; detectable intracranially but not intraorbitally on the affected side in Subject 3; and detected in both intracranially and intraorbitally on both affected sides in Subject 5. While the subarachnoid CN6 was visualized unilaterally in Subject 3 and bilaterally in Subject 5, in each

case it appeared small or dysplastic. In addition, in two of three affected orbits with absence of CN6 and in one of two affected orbits with presence of CN6, CN3 appeared to innervate or co-innervate the LR.

These MRI findings in DRRS confirm limited autopsy^{5,6} and electromyographic^{3,4,30} reports of CN6 aplasia with LR misinnervation by CN3 in DRS. In addition, MRI evidence of absence or marked hypoplasia of the subarachnoid CN6 appears to occur in DRRS with approximately the same frequency as in DURS2¹¹. These findings concord with prior MRI reports of occasional absence of the subarachnoid CN6 in sporadic DRS. Kim and Hwang have emphasized the frequent absence of CN6 ipsilateral to DRS type 1^{10,31} and type 3¹⁰, but the presence of CN3 ipsilateral to type 2¹⁰.

The ophthalmic phenotype and CN6 endophenotype of DRRS resemble those previously reported for DURS2, except for more frequent A or lambda strabismus patterns in the latter. The endophenotype of DRRS, however, is otherwise distinct from both DURS2 and from CFEOM1, the latter a congenital cranial dysinnervation disorder resulting from heterozygous missense mutations in *KIF21A*.

Low frequency of A pattern strabismus

We have noted frequent A pattern strabismus in both DURS2¹¹ and CFEOM1²⁴, and attributed this to LR misinnervation by a CN3 branch normally destined for the IR. In the present family with six DRRS subjects, only one had A pattern and one V pattern strabismus, and only the latter underwent MRI. While it was impossible to demonstrate directly the innervation to every EOM in DRRS, the relative infrequency of pattern strabismus suggests less frequent motor nerve misrouting to EOMs than in CFEOM1 and DURS2.

Absence of CN3 hypoplasia

While the MRI endophenotypes of both DURS2 and CFEOM1 feature CN3 hypoplasia, this was not the case for DRRS. Normal CN3 size in DRRS suggests that *SALL4* is not involved in CN3 development or maintenance. It also suggests that anomalous targeting of CN3 axons to the LR does not necessarily result in CN3 hypoplasia.

Absence of widespread structural abnormalities or hypoplasia of extraocular muscles

The only EOM structural abnormalities detected in DRRS were subtle splitting and hypoplasia limited to the deepest portion of the LR muscles in one subject. Only the inferior oblique muscle differed from controls in size, and was slightly smaller in two and slightly larger in one subject. This is in marked contrast to the endophenotype of both DURS2¹¹ and CFEOM1²⁴, in which we reported severe structural abnormalities and hypoplasia of EOMs. In DURS2, the LR often exhibits a striking longitudinal fissure and deep hypoplasia and disorganization¹¹, and the SR and SO can be hypoplastic. It has been hypothesized that structural abnormalities of the LR in DURS2 reflect intramuscular innervation abnormalities¹¹ that are presumably absent in DRRS. In CFEOM1, the rectus and oblique EOMs exhibit variable to profound hypoplasia, with occasionally severe dysplasia and occasional accessory EOM slips²⁴. Thus, although CN6 hypoplasia and aberrant LR innervation by a CN3 branch appears to be features common to all three of these congenital cranial dysinnervation disorders (CCDDs), the endophenotypic abnormalities of DURS2 and CFEOM1 are much more widespread than in DRRS.

Absence of optic nerve involvement

Quantitative MRI is useful for ON analysis²⁷, and has been applied to the CCDDs. In DURS2, ON cross sections are reduced about 25% from normal¹¹, while in CFEOM1 due to *KIF21A*

mutation is associated with 30 – 40% reduction in ON cross section²⁴. In contrast, ON size is normal in DRRS, suggesting that *SALL4* is not involved in ON development or maintenance.

Absence of widespread pulley abnormalities

Pulley disorders are associated with some forms of strabismus^{18,32}. Rectus EOM path abnormalities are associated with misplaced pulleys in craniosynostosis syndromes caused by mutations in *FGFR3*³³ in which orbital nerves and EOM volumes are normal. This contrasts with generally normal pulley positions in the current subjects with DRRS, and well as in DURS2¹¹ and in CFEOM1²⁴. Normal pulley positions despite abnormal innervation supports the idea that pulley abnormalities may be primary in some cases of strabismus^{21,34,35}. *SALL4* is apparently not involved in pulley development.

Vertical Saccade Initiation Failure

Subject 4 exhibited a deficit of visually evoked vertical saccades despite preservation of the vertical vestibulo-ocular reflex. This represents vertical saccade initiation failure, historically termed oculomotor apraxia, and is a central finding associated with metabolic disease and structural lesions of the cortex, brainstem, and cerebellum³⁶. Vertical saccade initiation failure was absent in the other subjects with DRRS studied here, and to our knowledge has not been reported in association with DRS.

Conclusion

DRRS resulting from a relatively selective heterozygous *SALL4* mutation CCDD affecting primarily CN6, with secondary misrouting of the inferior division of CN3 to normal or only mildly dysplastic EOMs. These ocular motor manifestations are associated with abnormalities of the radial bone, artery, and associated skeletal musculature. DRRS is not associated with ON abnormality, or widespread abnormalities affecting other ocular motor cranial nerves. The DRRS endophenotype is distinct from DURS2 and CFEOM1, reflecting presumably distinct molecular pathology.

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Fig. 1. Spectrum of hand abnormalities in Duane-radial ray syndrome. A, B. Subject 2 exhibits asymmetrical hypoplasia of the left thumb and thenar eminence. C, D. Subject 4 exhibits absence of the left thumb and radial bone, and has undergone surgical reconstruction of the right thumb.

Fig. 2.

Subject 1 exhibited Duane syndrome of type 3 in the right eye, and type 1 in the left eye. Note limited abduction and adduction of the right eye, upshot of the right eye in adduction, and narrowing of the right palpebral fissure in adduction. Note limited abduction and supraduction of the left eye. There was palpebral fissure narrowing and globe retraction in adduction bilaterally. Eyelids were manually elevated in the lower row only as the lids would otherwise have covered the eyes.

Fig. 3.

MRI of orbits of Subject 5, who exhibited bilateral type 3 DRS. This subject had the most severe extraocular muscle abnormalities of the subjects with DRS, consisting of mild longitudinal fissuring of the lateral rectus (LR) muscles, and hypoplasia of the deep portion of the left LR. Image planes 2 mm thick, skipping planes between those illustrated. CN3 – inferior division of oculomotor nerve. IR – inferior rectus muscle. LPS – levator palpebrae superioris muscle. MR – medial rectus muscle. ON – optic nerve. SO – superior oblique muscle. SR – superior rectus muscle.

Fig. 4. Heavily T2 weighted MRI of the pons and subarachnoid portion of the abducens nerve (CN6) in subjects with DRRS. Images are 1 mm thick, parallel to the plane of the optic chiasm, and were chosen from sets of contiguous image planes. Note unilateral absence of CN6 in Subjects 2 and 6, hypoplasia of left CN6 in Subject 3, and dysplasia of CN6 in Subject 5.

Table 1

Subject Characteristics

Subject	Age (yrs)	Sex	Absent Radial Pulses		Thenar Hypoplasia		Corrected Visual Acuity		Horizontal Alignment	DRS Type ^a		MRI
			R	L	R	L	Right (logMAR)	Left (logMAR)				
1	13	M	+	+	+	+	-0.05	0.05	A-ET	3	1	No
2	42	M	+	+	+	+	-0.10	-0.20	ET	3	-	Yes
3	46	M	-	-	-	-	-0.05	-0.05	ET	-	1	Yes
4	45	F	+	-	+	+	-0.05	-0.05	Orthotropic, limited vertical versions	3	3	No
5	45	M	+	+	+	+	-0.10	0.05	V-VT	3	3	Yes
6	68	F	-	-	+	+	0.40	-0.05	Orthotropic	3	-	Yes
Mean	45						0.01	-0.04				
SEM	8						0.02	0.03				

+ finding present. -: finding absent. ET: esotropia. A-ET: "A" pattern esotropia. V-VT: "V" pattern exotropia. ND: not examined. SEM: standard error of the mean.

* Clinical classification of Huber: type 1 - limitation of abduction only; type 2 - limitation of adduction only; and type 3 - limitation of both ab- and adduction^{3,28}

Subjects contributed data from both orbits where available. Volumes for rectus EOMs include contributions from six contiguous images planes extending posteriorly beginning at the globe-optic nerve junction. There were no significant differences among the three groups ($P > 0.05$).

Table 2
Muscle Volumes in Subjects With DRRS and DURS2-linked DRS

Muscle	Control Subjects N = 9			Subjects with DRRS N = 4			Subjects with DURS2 N = 7		
	Volume (mm ³)	Mean	SEM	Volume (mm ³)	Mean	SEM	Volume (mm ³)	Mean	SEM
Medial Rectus	395	16	16	401	28	12	376	12	12
Superior Rectus	370	32	32	411	26	16	374	16	16
Lateral Rectus	428	15	15	460	47	17	385	17	17
Inferior Rectus	385	12	12	429	20	15	387	15	15