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Bilateral congenital vertical gaze disorders: congenital muscle fibrosis or congenital central nervous abnormality?

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Abstract Congenital disorders of vertical gaze are uncommon and current terminology such as double elevator palsy, congenital fibrosis syndrome and congenital ocular motor palsy poorly reflect the underlying pathophysiology. Congenital fibrosis syndrome appears to be the most common of these disorders. We describe nine additional patients with congenital vertical motility restrictions who fit the descriptions of this syndrome. Six of the patients had positive family histories and came from consanguineous marriages. Numerous clinical features, including supranuclear disturbances of ocular motility, point to a central etiology rather than a primary muscle disorder, as 'congenital fibrosis syndrome' suggests.

Key words Congenital fibrosis syndrome; vertical gaze; supranuclear disorders of gaze; extraocular muscle

Introduction

Vertical ocular motility disorders can involve upgaze or downgaze in isolation or any combination of both with or without involvement of the horizontal eye movements. The most frequent cause of congenital bilateral restrictions of vertical gaze is the congenital fibrosis syndrome (CFS) which is further characterized by ptosis and variable impairment of horizontal eye movements. Additional features include divergent strabismus and abnormal head position, especially chin elevation.[1-3] Attempts at defining subgroups have been made,[4-7] but considerable overlap and intrafamilial variability exists (Table 1). The nine patients described in this paper had typical signs of CFS, most fitting the description of a 'general fibrosis' subtype. The traditional interpretation of the restrictive and fibrotic muscle changes was based on the assumption of a primary myopathic process. Detailed analysis of our patients' motility patterns, however, suggests that the underlying cause of CFS is a central disorder involving predominantly structures mediating vertical gaze.

Patients and methods

The patients attended King Khaled Eye Specialists Hospital (KKESH) and University Hospitals, Riyadh, over a six-year period. They presented from infancy through adolescence and were coded

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TABLE 1. Subtypes of congenital ocular fibrosis syndrome.

General fibrosis syndrome
Fibrosis of the inferior rectus with blepharoptosis
Fibrosis of the vertically acting muscles and nystagmus
Strabismus fixus
Ocular muscle fibrosis, blepharoptosis, and enophthalmos
Vertical retraction syndrome

under various diagnoses such as Parinaud's syndrome, third nerve palsy, and Duane's syndrome. Three patients underwent eye muscle surgery with intraoperative forced duction tests. Biopsies of resected muscles were obtained. The specimen originated from clinically uninvolved muscles only.

Results

AGE AND SEX The age at presentation varied from 10 months to 17 years. Four patients were female and five male (Table 2).

FAMILY HISTORY Four patients, two brother and sister pairs, had a positive family history. The parents were close relatives suggesting a recessive mode of inheritance. The parents of two more patients were also related, one with a family history of ptosis (Table 2). The family history of three patients was unrevealing.

OCULAR MOTILITY FINDINGS

Vertical gaze All of the patients had bilateral limitations of upgaze. Eight had −4 and one had −3 limitation on a scale of 4. Downgaze was involved in six of the nine patients. Three had −4 and one had −2 limitation in the downward direction. Two more patients had −2 to −3 limitation of downgaze in abduction more so than in adduction. One patient had overactivity of the superior obliques in both eyes. Restrictions of vertical gaze were mostly symmetrical in all patients (Table 3).

Horizontal gaze Limitations of horizontal gaze were less frequently observed. Three patients had normal horizontal eye movements in both eyes. Three had limitations involving one eye only, one with −2 limitation of ad-

TABLE 2. Patient analysis.

No.	*Sex*	*Age (years)*	*Family history*
1	M	1	Parents are second cousins
2	M	1 4/12	Parents are second cousins; sister has a similar condition (patient 3)
3	F	7	Sister of patient 2
4	M	4	Negative
5	F	5	Parents are first cousins; maternal grandmother had ptosis
6	F	6	Negative
7	F	9	Parents are first cousins; sister of patient 8
8	M	10/12	Brother of patient 7
9	M	17	Negative

No.	*Vertical gaze*		*Horizontal gaze*		*Other eye movement disorders*
	UG	*DG*	*ADD*	*ABD*	
1	−4	−2	−	−1(OD)	Bilateral convergence on attempted upgaze
2	−4	−	−	−	Esotropia OS on attempted elevation
3	−4	−2(T)	−	−	Bilateral convergence on attempted upgaze; +2 overaction of the superior obliques OU
4	−4	−	−1.5(OU)	−2(OU)	Bilateral convergence on attempted upgaze
5	−3	−4	−2(OD)	−3(OD)	Narrowing of the palpebral fissure (PF) on adduction OU with retraction of the globe OD; widening of the PF on abduction OS
6	−4	−2/3(T) −1/2(N)	−2(OS)	−	Bilateral convergence on attempted elevation
7	−4	−4	−4(OU)	−2(OS)	Bilateral retraction on horizontal and vertical gaze
8	−4	−4	−4(OU)	−4(OD) −1(OS)	Globe retraction OD on attempted movement
9	−4	−	−	−	−

TABLE 3. Eye movement analysis. UG, Upgaze; DG, Downgaze; ADD, Adduction; ABD, Abduction; −1 to −4, Limitations of eye movements out of a scale of 4; −2/3 = −2 to −3; −1/2 = −1 to −2; T, Temporally; N, Nasally.

duction affecting the left eye, another with −1 limitation of abduction affecting the right eye. A third patient had involvement of both adduction and abduction of the right eye (−2 to −3). The remaining three patients had involvement of both eyes varying from −1.5 to −4 (Table 3).

Convergence, retraction, and narrowing of the palpebral fissure In four patients, attempts at shifting the eyes in the upward direction resulted in bilateral adduction (pts. 1, 3, 4, 6) (Table 3). Only one of these patients had a full range of horizontal eye movements. A fifth patient showed only unilateral adduction of the left eye while attempting to look up (pt. 2). Retraction of the globe and palpebral fissure narrowing occurred during horizontal gaze shifts in patients with the most severely restricted horizontal eye movements (pts. 5, 7, 8). Both eyes retracted on lateral eye movements in pt. 7. Pts. 5 and 8 had only unilateral globe retraction of the right eye, limited to adduction in pt. 5. However, in this patient the right and left lid fissure narrowed as she attempted adduction. In addition, the left palpebral fissure widened on abduction of the left eye (Figs 1,2).

Strabismus Horizontal deviations in primary position were present in six patients. Two had variable angle esotropia/exotropia (ET/XT) for near and distance. One had variable angle esotropia of 0-45 prism diopters (pd) for distance and 0-20 pd at near. The remaining three had XT, two with variable angles. In one of these patients, the angle of XT varied between 0 and 60 pd (Table 4).

ASSOCIATED OCULAR FINDINGS Amblyopia was common and high myopia was present in two patients. Another patient had high hyperopia and anisometropia (Table 4). Seven patients had bilateral ptosis which was mostly severe. This was associated with blepharophimosis in one patient. Pupillary reflexes were normal in all, but one patient who had an immobile, dilated pupil on the right. Nystagmus was present in two patients. Eye movement recordings were not obtained.

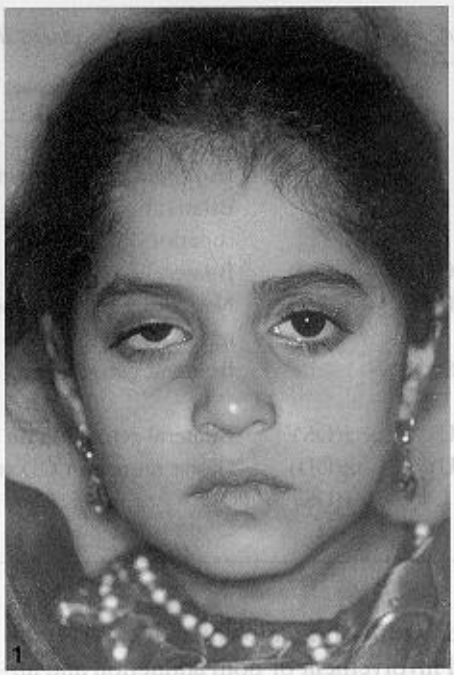
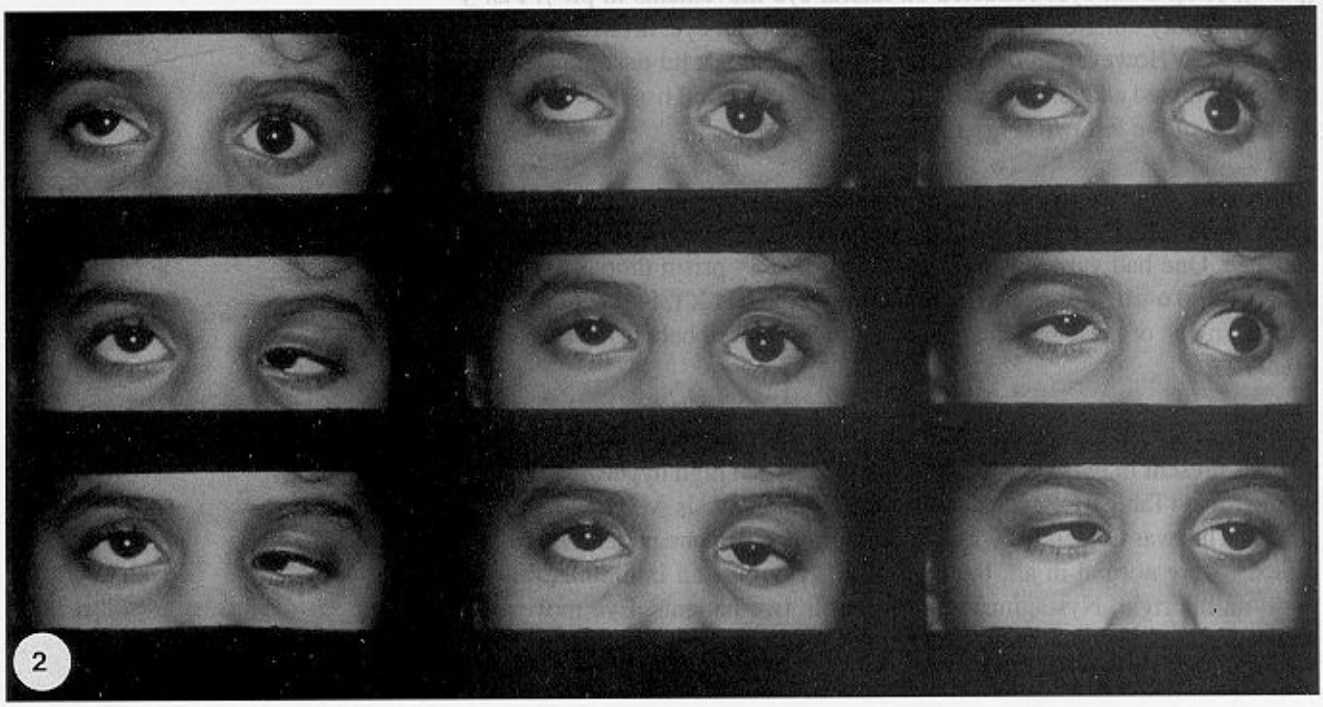


Fig. 1. Patient 5. Ptosis with hypertropia in the primary position OD.

ABNORMALITIES OF HEAD POSITION Head position was abnormal in eight of nine patients (Table 4). Chin elevation was present in six patients, chin depression in one, and six patients turned and tilted their heads. This appeared to facilitate fixation with the better eye or of the eye with the larger range of horizontal movements. Chin elevation occurred mostly in patients with intact downgaze, but did not correlate with the presence of ptosis.

Fig. 2. Patient 5 showing the nine positions of gaze. Notice the narrowing of the palpebral fissure on adduction and widening on abduction, particularly in the left eye.



No.	*Strabismus*	*Ocular findings*	*Head position*
1	ET OD(0-30) XT at times	Nystagmus; ptosis; blepharophimosis; myopia; blurred disc margins OU	Chin elevation/left face turn
2	None	–	Chin elevation
3	None	Ptosis; amblyopia	Chin elevation/right face turn
4	None	Ptosis; nystagmus; amblyopia OU	Chin elevation/right head tilt
5	ET/XT OD 40 ET–20 XT	Amblyopia OD>OS; eccentric fixation OD; partial ptosis OD; pupils normal	Normal
6	XT 0-60 OS	Amblyopia; no ptosis; prefer OD, holds with difficulty	Chin elevation/right face turn
7	XT 90 OD	Myopia and anisometropia; amblyopia OS>OD; ptosis OU; no Bell's	Right face turn/chin depression
8	XT 60-90 OD HT 15	Ptosis OU; pupils dilated OD; miosed OS; alternate fixation; no Bell's	Shifting head Right position/left face turn
9	ET 0-45 distance 0-20 near	Ptosis OU OS>OD; amblyopia; high hyperopia and anisometropia; amblyopia; no Bell's	Chin elevation

TABLE 4. Strabismus, ocular findings, and head positions. Strabismus measurements are in prism diopters.

SURGICAL FINDINGS Patient 3: At age seven, this girl underwent bilateral inferior rectus recession. Intraoperative forced duction testing (FDT) showed restriction of elevation of both eye, in the rightward more than leftward direction. The superior and horizontal recti were normal on FDT.

Patient 6: This six-year-old girl required recession/resection of the horizontal recti OS for –4 adduction limitation. In addition, both inferior recti were recessed. Intraoperative FDT revealed limitation of elevation in both eyes (–2 to –3 OD and –3 OS). Depression of the globes revealed mild restriction of –0.5 OD and –1 OS. The left lateral rectus and both inferior recti were fibrotic and tight in situ.

Patient 7: This nine-year-old girl (Figs 3,4) had –2 limitation of elevation and –0.5 limitation of depression of the right eye on intraoperative FDT. Horizontal ductions were normal. The left eye had –4 limitation of elevation, –3 limitation of depression, and –4 limitation of adduction. Abduction was

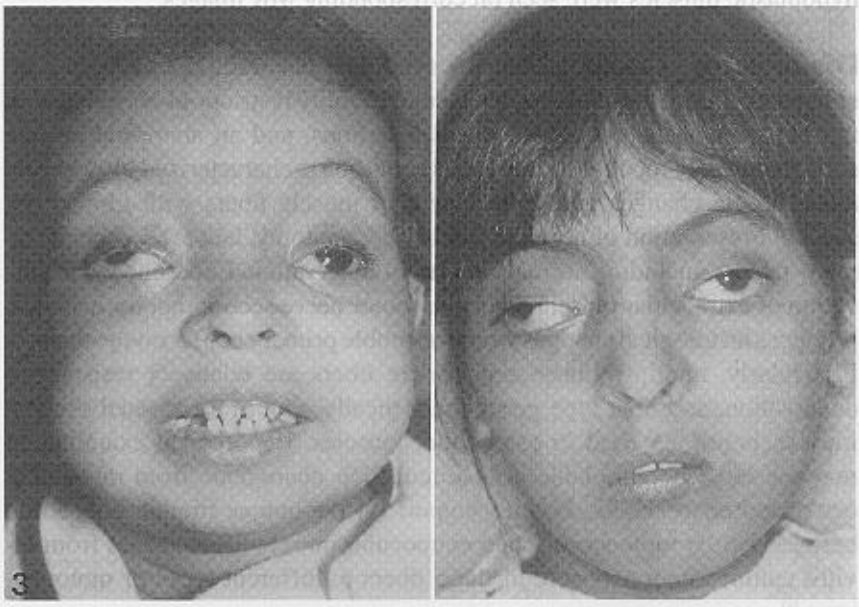


Fig. 3. Case 7 sister (on the right side) and Case 8 brother with bilateral ocular motility involvement.

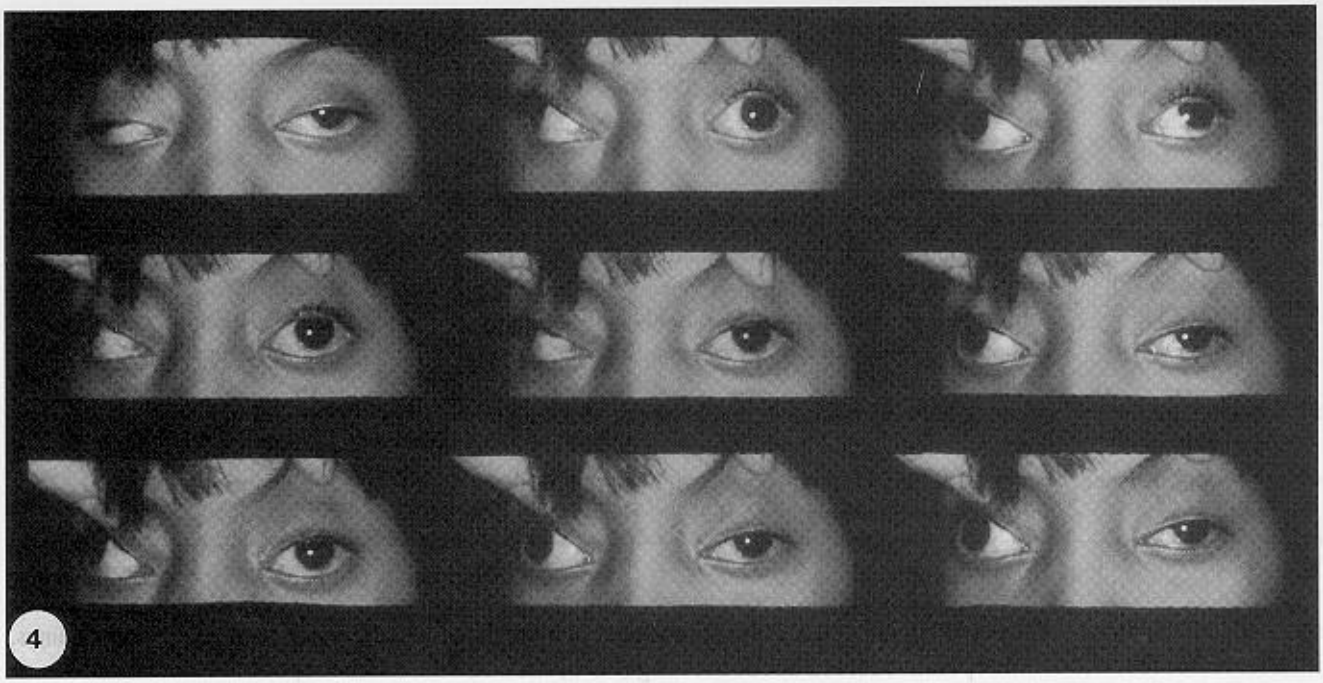


Fig. 4. Patient 7 showing the nine positions of gaze. The patient fixed with the left eye in a mid-abducted position with significant right face turn.

normal. In this patient and the other two operated patients, the degree of muscle tightness on FDT did not always correspond with the clinically observed degree of movement restriction.

Muscle tissue was only obtained during resection of the medial recti of patients 6 and 7. The muscles were normal clinically and histologically.

SYSTEMIC FINDINGS One of the nine patients was mentally retarded and showed dysmorphic features including low set ears and blepharophimosis. His MRI indicated possible cerebellar hypoplasia. The other patients had no associated neurological or systemic abnormalities. Except for one, all had CTs (6 patients) or MRI (1 patient). These studies revealed no CNS abnormalities. In one patient, the CT indicated agenesis of the superior recti, but hypoplastic muscles were seen on corresponding MR images.

Discussion Congenital fibrosis syndrome has traditionally been considered a primary muscle disorder. Ocular motility restrictions correlate with muscle hypoplasia, displaced scleral insertions, and an abnormal muscle substructure. Histopathologically, this condition is characterized by degenerative muscle changes and replacement of muscle fibers with fibrous tissue.[2,4,5] Preservation of normal muscle fiber anatomy, however, depends on many factors, including normal patterns of innervation. Experimental denervation of extraocular muscle by ocular motor nerve sectioning, for instance, produces histological changes which resemble primary ocular myopathies.[8,9] Particularly, multiply innervated muscle fibers are relatively resistant to denervation, and fiber type grouping, typically seen in denervated skeletal muscle, is not apparent in extraocular muscles. Histological examination may therefore be unreliable in distinguishing neurogenic from myopathic ocular motor weakness. Further support for the unique trophic interaction between ocular motoneurons and extraocular muscle fibers comes from in-vitro cultures with exposure of these fibers to different types of motoneurons.[10]

In humans, pathological studies of Duane's syndrome have provided clear evidence that innervational deficiencies can cause fibrotic muscle changes. Most cases are due to a congenital anomaly of innervation which correlates with aplasia of the sixth nerve nucleus and the nerve itself.[11] In Duane's syndrome, innervation of the lateral rectus is provided by the oculomotor nerve causing the pathognomonic cocontraction of the medial and lateral recti with globe retraction on adduction. Additional synkinetic phenomena such as eyelid elevation on attempted abduction and twitch abduction on attempted upgaze have a similar physiological basis.[12] One of our patients demonstrated an identical anomaly when abducting the left eye which caused ipsilateral lid elevation (Fig. 2). Other cocontraction phenomena were also common amongst our patients with CFS. The three subjects with the most severe restrictions of horizontal eye movements all showed globe retraction, one on adduction only and two with attempted gaze shifts in all directions (Table 3). In the absence of vertical gaze anomalies, such patients (particularly patient 5) could be diagnosed as Duane's syndrome, type III.

Thus, CFS may share anatomical similarities with Duane's syndrome, but more extensive involvement of brainstem structures involved in ocular motor control must exist. Ptosis, loss of up- and downgaze, pupilloplegia, and numerous cocontraction phenomena suggest involvement of the third nerve nuclei and supranuclear structures involved in the central control of vertical eye movements. In humans, burst neurons for vertical gaze are located in the rostral interstitial nucleus of the medial longitudinal fascicle (riMLF).[13,14] Lesions of this nucleus or its efferents to the oculomotor subnuclei cause vertical eye movement restrictions with variable involvement of up- and downward gaze.[15] The nearby nucleus of Cajal (NC) participates in the control of vertical pursuit movements, mediates vestibular input to the oculomotor nuclei, and functions as a neural integrator of vertical and torsional gaze. The anatomical proximity of these structures suggests a shared vulnerability to congenital malformations which may involve the nuclei themselves and their connections. The complexity of the functional interactions between supranuclear structures and the ocular motor nerves may account for the highly variable expressions of vertical and horizontal gaze abnormalities in CFS.

Clinicopathological correlation and precise eye movement recordings are presently lacking, rendering ideas about specific patterns of neural misdirection speculative. Innervational abnormalities are probably compounded by secondary changes in muscle structure. Therefore, mechanical factors could contribute to some motility disturbances of CFS. Tightness of the inferior recti, for instance, may cause convergence on attempted upgaze in a similar fashion as the increased tension of cocontracting horizontal recti causes up- and downshoot phenomena in Duane's syndrome.[16]

Additional observations in our patients and in other published series provide further support for a central pathogenesis of CFS. Variable angle strabismus occurred in four of the nine patients described here, consisting of exotropia between 0-60 pdpt (patient 6), variable esotropia (patient 9), and variable ET-XT in two additional patients. Purely mechanical factors appear insufficient to explain this variability which more likely reflects innervational disturbances. Furthermore, the degree of limitation of ocular movements in our patients did not always correlate with the degree of tightness of the agonist or antagonist muscle, as indicated by the intraoperative FDT.

Nystagmus, another indicator of central ocular motor disturbance, was present in two of nine patients in this series and in all affected members of a recently described multigenerational family with CFS.[7] Results of neuroimaging have only been reported on relatively small numbers of patients. Abnormalities such as asymmetrical ventricular size[7] and cerebellar hypoplasia (patient 1) further hint at the possibility of brain malformation.

Variable patterns of inheritance have been described in CFS, including mostly dominant and some recessive cases[17] as well as sporadic occurrences. The autosomal dominant variant of CFS has recently been mapped to chromosome 12*.[18] In this series, four patients came from consanguineous marriages suggesting a recessive mode of inheritance. Patients 7 and 8, for instance, are from a consanguineous first marriage with a total of four children. The father and his second, unrelated wife had an additional ten children which were all unaffected.

* For further information on genetic testing, contact Drs. E. Engle or A. Beggs from The Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA. Tel. 617-735-7574, Fax 617-735-7588.

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