Graefe's Arch Clin Exp Ophthalmol
(2003) 241:546–553

CLINICAL INVESTIGATION

DOI 10.1007/s00417-003-0703-z

Christina Pieh
Hans Hilmar Goebel
Elizabeth C. Engle
Irene Gottlob

Congenital fibrosis syndrome associated with central nervous system abnormalities

Received: 7 August 2002
Revised: 9 April 2003
Accepted: 7 May 2003
Published online: 18 June 2003

C. Pieh
Department of Strabismus
and Neuroophthalmology,
Kantonsspital St. Gallen,
St. Gallen, Switzerland

H. H. Goebel
Department of Neuropathology,
Johannes Gutenberg University of Mainz,
Mainz, Germany

E. C. Engle
Departments of Genetics and Neurology,
Children's Hospital Boston,
Harvard Medical School,
Boston, Massachusetts, USA

I. Gottlob (✉)
Department of Ophthalmology,
Leicester Warwick Medical School,
Leicester Royal Infirmary,
Leicester, LE1 5WW, UK
e-mail: ig15@leicester.ac.uk
Tel.: +44-116-2586203
Fax: +44-116-2558810

Abstract *Background:* Congenital fibrosis of extraocular muscles (CFEOM) is a complex strabismus syndrome that typically occurs in isolation and results from dysfunction of all or part of cranial nerves III (CNIII) and IV (CNIV) and/or the muscles that these nerves innervate. Only a few patients with CFEOM and additional central nervous system malformations have been reported. We describe four additional patients with CFEOM associated with central nervous system (CNS) abnormalities. *Methods:* Four patients who presented with congenital restriction of eye movements in association with neurological abnormalities underwent complete ophthalmological examination including electroretinography (ERG) and eye movement recordings. Neurological examinations, neuroradiological studies, muscle histology, chromosomal and genetic linkage analysis were performed. *Results:* Clinical examination and forced duction testing confirmed that all four patients met criteria for CFEOM; all had congenital restrictive ophthalmoplegia primarily affecting extraocular muscles innervated by the oculomotor nerve. Two brothers had CFEOM and Marcus Gunn jaw winking. In each of the four cases, CFEOM occurred in association with one or several neuroradiological findings, including agenesis of the corpus callosum, colpocephaly, hypoplasia of the cerebellar vermis, expansion of the ventricular system, pachygyria, encephalocele and/or hydrancephaly. *Conclusions* We present four cases of CFEOM in association with CNS malformations that confirm that CFEOM can be part of a more complex neurological dysfunction and provide further support to a neurogenic aetiology for this disorder. We also describe for the first time the coexistence of CFEOM and Marcus Gunn jaw winking in two siblings. This suggests a genetic mechanism. Aberrant innervation supports primary developmental abnormality of cranial nerves in CFEOM.

Introduction

Congenital fibrosis of extraocular muscles (CFEOM) is a relatively rare disorder characterised by congenital restrictive ophthalmoplegia and ptosis, frequently with the primary position of the eyes fixed in downgaze, leading to a compensatory backward tilt of the head. Patients may have aberrant convergent eye movements on attempted upgaze [1]. This syndrome was first described in 1879 by Heuk, who showed on post-mortem examination that the extraocular muscles were fibrotic and abnormally inserted [2]. There has been controversy as to whether the primary pathology of CFEOM is intrinsic to the extra ocular muscles (EOM) (myogenic) or secondary to faulty neuronal connections of the EOM (neurogenic). A primary myogenic aetiology has been suggested by a "fibrotic" feel to the EOM at surgery, and by reports of light- and electron-microscopy studies of EOM

biopsies showing replacement of myofibres by fibrous connective tissue and collagen [3]. Studies of the molecular genetic and neuropathological bases of CFEOM, however, support a neurogenic cause for this disorder.

CFEOM is frequently inherited and, to date, three CFEOM phenotypes and three *FEOM* genetic loci have been identified. Most families whose phenotypes map to the *FEOM1* locus on chromosome 12 have dominant CFEOM1 [4, 5]. In these families, all affected members have bilateral ptosis and globe infraduction, referred to as "classic CFEOM". Neuropathological examination of an affected member of a CFEOM1 family linked to the *FEOM1* locus revealed that the superior rectus and levator muscles, but not the inferior rectus, were fibrotic, and there was an absence of the superior division of the oculomotor nerve and of the corresponding oculomotor subnuclei in the midbrain [6]. These findings are consistent with a primary neurogenic defect in the development of specific oculomotor subnuclei. Families whose phenotypes map to the *FEOM2* locus on chromosome 11q13 have recessive CFEOM2 with bilateral exotropia [7]. The affected members of these families harbour homozygous mutations in the *ARIX (PHOX2A)* gene [8]. *Arix* encodes a transcription factor necessary for the development of the oculomotor and trochlear nuclei [9, 10], establishing that this form of CFEOM is neurogenic in aetiology. Lastly, families whose phenotype maps to the *FEOM3* locus on chromosome 16qter have dominant CFEOM3 with variable ptosis and abnormalities of vertical gaze [11]. The sporadic occurrence of CFEOM has also been reported [1].

Although CFEOM is typically unaccompanied by any other abnormalities, rare reports of patients with CFEOM in association with central nervous system (CNS) disorders also lend support to a neurogenic aetiology. Previous reports include four patients with sporadic CFEOM in association with Marcus Gunn jaw-winking phenomenon (trigemino-oculomotor synkinesis characterised by upper eyelid ptosis associated with elevation of the ptotic eyelid when the ipsilateral pterygoid muscle contracts) [12, 13], a case of CFEOM with synergistic divergence [13], two patients with CFEOM and Joubert's syndrome [14, 15], and a mother and two children with CFEOM associated with cortical dysplasia and maldevelopment of the basal ganglia [16]. Recently, a case of CFEOM and elevation of one eye during tooth brushing due to aberrant regeneration between the nerve to the superior rectus and the trigeminal nerve was described [17]. In this paper we present four additional clinical cases of congenital ocular fibrosis syndrome associated with CNS abnormalities.

Materials and methods

Clinical features

We identified and examined four boys in three unrelated families between the ages of 3 weeks and 12 years who presented with congenital restriction of eye motility and CNS malformations. Informed consent for all examinations was obtained from the patients' parents. All subjects underwent complete ophthalmological examination. Visual acuity was tested using the preferential looking (PL) method, where PL acuity cards were positioned at a test distance of 38 cm. Electroretinography (ERG) recordings were performed according to ISCEV standards [18] in two of the patients. In two patients, eye movements including horizontal and vertical fixations, saccades, and pursuit movements were recorded by electro-oculography (EOG) using the EOG Vision Monitor System (Metrovision, Villeneuve d'Ascq, France) with Stat-Trace II electrocardiographic electrodes (Niko Med USA, New Brunswick, NJ). Eye position was recorded on a digital computer with a sampling rate of 230 Hz. Data were converted from analogue to digital with 12 bits.

In three of the patients magnetic resonance imaging (MRI) scans of the brain were obtained on a 1.5 T magnet. In one patient computed tomography (CT) of the brain was performed. EOM biopsy specimens were obtained from all patients during strabismus surgery, taken between about 10 and 13 mm from insertion of the inferior rectus muscle. For each biopsy a small sample of tendon, muscle and conjunctiva was removed and snap frozen in liquid nitrogen. Histology was evaluated with haematoxylin–eosin, trichrome and Elastica van Gieson staining.

Molecular analysis

Chromosomal analysis of patient 1 was performed. Blood samples were collected and lymphocyte DNA was extracted from the two brothers (patients 1 and 2) and five additional members of their family. Linkage studies and haplotype analysis were conducted using polymorphic DNA microsatellite markers. To assess linkage to each locus, the following markers were analysed: (1) *FEOM1* locus [5] markers *AFM136xf6*, *D12S1648*, *D12S345*, *D12S1692*, *GATA63D01*, *D12S59*, *D12S1048*, and *D12S1668*; (2) *FEOM2* locus [7] markers *D11S1337*, *D12S4196*, *D11S4162*, *D11S1314*, and *D11S13692*; (3) *FEOM3* locus [11] markers *D16S486, D16S2621*, *D16S3121*, *D16S3063,* and *D16S303*. Primer sequences are available from Genome Data Base (http://gdbwww.gdb.org). Primers were purchased from Genosys Biotechnologies. Amplification and analysis of repeat polymorphisms were performed as reported previously [4, 5, 6].

Statistical analysis

Lod scores were calculated with the Fastlink version 3.0 package of programs under the assumption of autosomal dominant inheritance with complete and 90% penetrance (*FEOM1*, *FEOM3*), and autosomal recessive inheritance with complete penetrance (*FEOM2*). Lod scores were calculated twice, once assuming that the maternal uncle was affected (2) and once assuming that he was unaffected (1). In both calculations, the affected brothers were scored as affected (2), and all the remaining members of the family were scored as unaffected (1). Data on the population incidence of the mutation is unavailable; for lod score calculations, we used a disease incidence of 1/1000 births and 10 marker alleles of equal frequency, as done previously [7, 11].

Results

Patient 1

This 21-month-old boy initially presented to medical attention at 2 months of age because of bilateral ptosis and

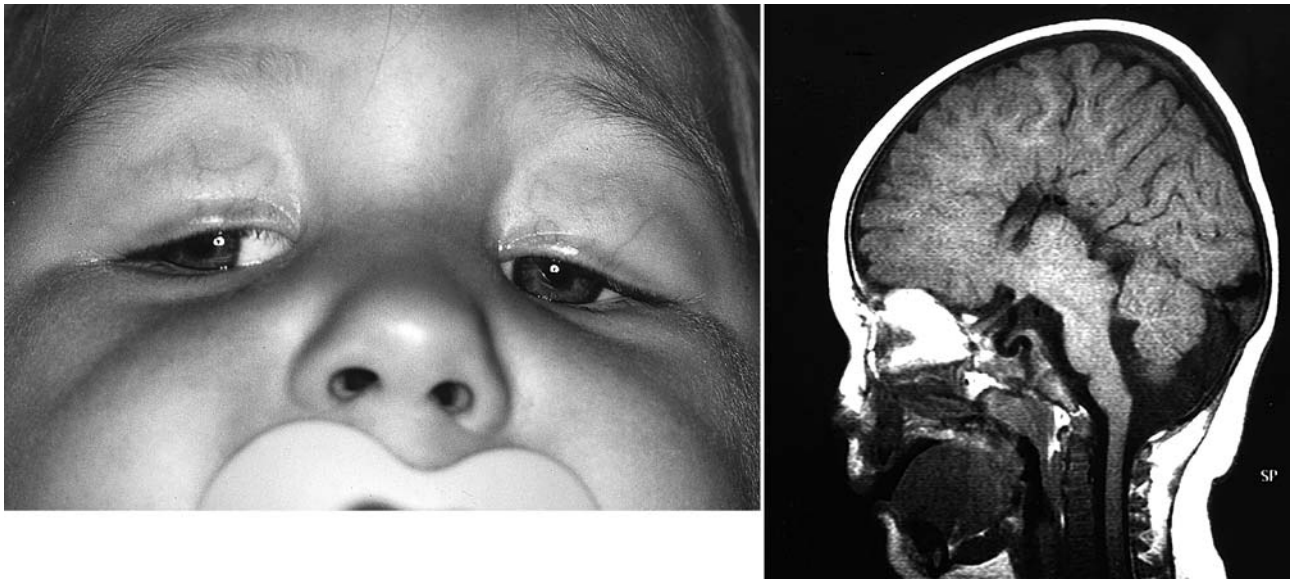

Fig. 1 Patient 1. *Left*: The patient presents with a chin-up head position and bilateral ptosis and exotropia. *Right*: Cerebral MRI in the sagittal plane of patient 1 showing agenesis of the corpus callosum and vermis hypoplasia

presumed nystagmus noted shortly after birth. His younger brother (patient 2) was also affected. Their nonconsanguineous parents, grandparents, and an older brother were not affected. On ophthalmological examination, all of them had normal vision, full eye motility and no ptosis. A maternal uncle reportedly had ptosis but was not examined by the authors. Pregnancy and birth were normal. Ophthalmological examination at 2 months of age revealed that at rest his eyes were in downgaze with a large exotropia (Fig. 1, left). He had reduced ocular motility in all directions of gaze, he could not raise his eyes above the horizontal midline, and upgaze could not be elicited. On attempted upgaze pronounced convergence eye movements which mimicked nystagmus could be seen. A bilateral Marcus Gunn jaw winking syndrome was present which caused pronounced rhythmic movements of both upper eyelids while the patient was sucking on his bottle. Cycloplegic refraction showed hyperopia of +2.0 sph in both eyes. At 4 months of age grating visual acuity was normal in the right eye (0.15), and decreased (0.04) in the left exotropic eye, probably due to amblyopia. Fundus examination and ERG were normal. Eye movement recordings by EOG showed convergent eye movements of high amplitude and low frequency on attempted upgaze, mimicking dysconjugate nystagmus, and smaller and faster convergence movements on primary gaze (Fig. 2). Neurological examination revealed microcephaly, mental and physical retardation and muscle hypotonia. MRI showed agenesis of the corpus callosum, vermis hypoplasia (Fig. 1, right) and colpocephaly, a dilation of the occipital horns due to absence of the corpus callosum splenium. The brainstem had an abnormal configuration in the region of the pons without a distinct tectum. At 21 months of age a large recession of both inferior rectus muscles was performed to correct a pronounced retroflexed head position. Traction tests were positive for restriction. The muscles felt stiff and were thinner than normal. Histological examination of inferior rectus muscle biopsy revealed an augmentation of collagen and fibrous tissue and a reduced number of atrophic muscle fibres. Chromosomal analysis showed a normal karyotype of 46XY. Results of genetic linkage analysis are discussed below.

Patient 2

The younger brother of patient 1 had unilateral ptosis of the left eye at birth (Fig. 3, left). Ophthalmological examination, first carried out at the age of 3 weeks, revealed an ocular motility pattern similar to that of his brother. The eyes were hypotropic and exotropic at rest. He could not raise his eyes above the horizontal midline, and it was not possible to evoke upgaze voluntarily or by vestibular ocular reflex. Convergent horizontal eye movements and an exotropia of the left eye were observed on attempted upgaze. Marcus Gunn jaw-winking phenomenon was present on the left side. Cycloplegic refraction showed hyperopia of +4.25 sph with a astigmatism of +0.5 cyl/180° in the right eye and hyperopia of +4.75 sph with astigmatism of +0.75 cyl /180° in the left eye. Fundus examination revealed a decreased size of the optic disc in both eyes and a hypopigmentation of the fundus periphery. ERG was normal. Imaging by cranial ultrasound and MRI revealed agenesis of the corpus callosum, vermis hypoplasia (Fig. 3, right) and colpocephaly. The brainstem was underdeveloped. At

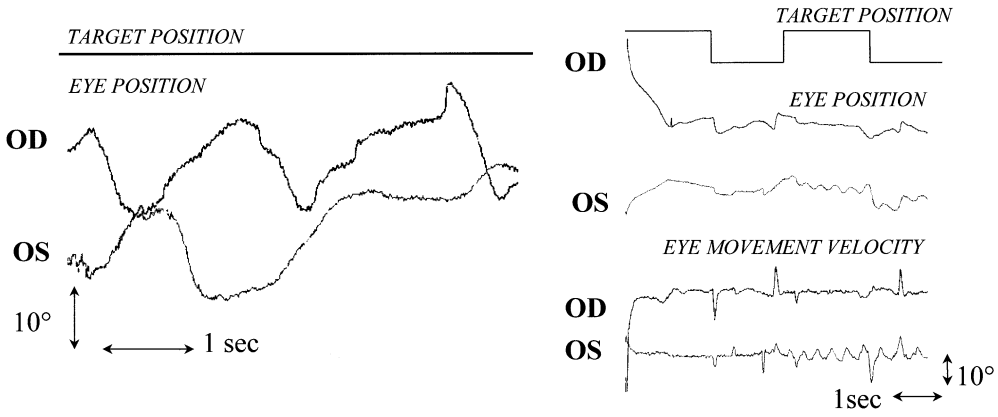

Fig. 2 Patient 1 *Left*: Original EOG recordings of horizontal position of the right eye (*top trace*) and left eye (*bottom trace*) of patient 1 on attempted upgaze. Convergent eye movements mimicking nystagmus of up to 40° and a frequency between 0.5 and 1 Hz can be observed. *Right*: Original EOG recordings of horizontal position of the right eye (*top trace*) and left eye (*bottom trace*) of patient 1 during horizontal saccades and downgaze. Convergent eye movements are less pronounced than in attempted upgaze. Amplitudes of 2–4° and frequencies of up to 4 Hz can be seen. Upward movements on recordings depict movements towards the right and downward tracings, movements towards the left

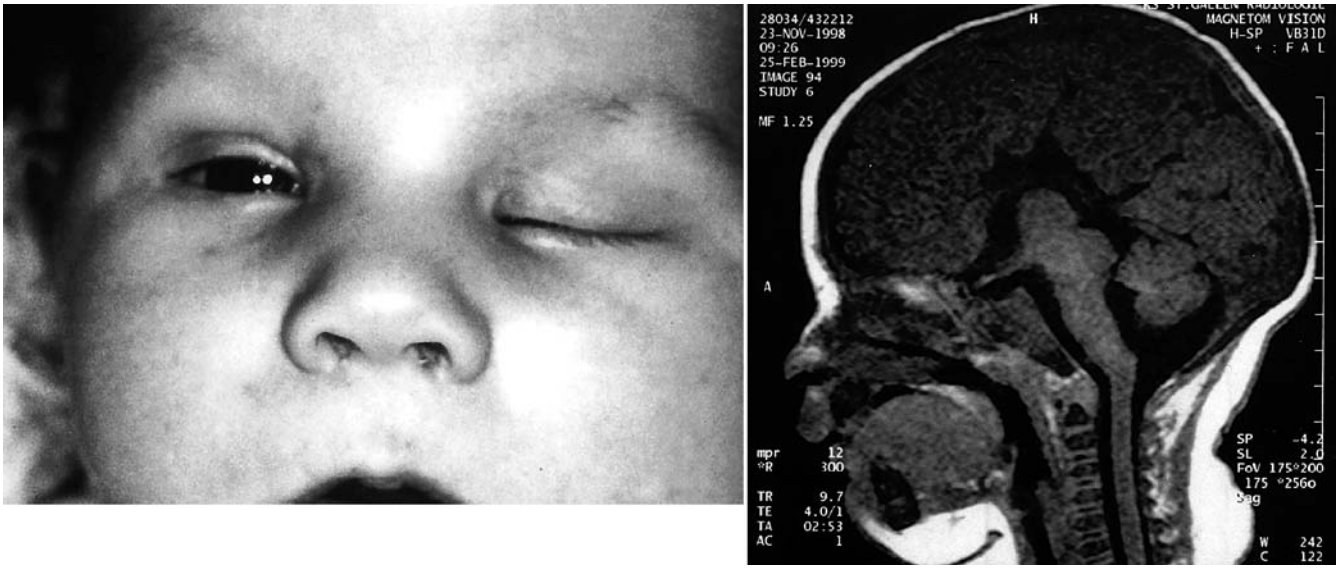

Fig. 3 Patient 2 *Left*: The patient presents at birth with ptosis of the left eye and exotropia. *Right*: Cerebral MRI in the sagittal plane showing agenesis of the corpus callosum and vermis hypoplasia

7 months of age a large recession of both inferior rectus muscles was performed to correct the abnormal head position with elevation of the chin. Traction test was positive for restriction, muscles were thinner than usual and felt stiff. Histological examination of inferior rectus muscle showed an increase in collagen and fibrous tissue and a numerical decrease and atrophy of muscle fibres. Results of genetic linkage analysis are discussed below.

Patient 3

A 12-year-old boy presented with a history of neonatal asphyxia, microcephaly and psychomotor retardation. Examination showed his eyes fixed in downgaze with chin up and to the left, absence of ptosis, esotropia of the right eye, and reduced eye motility in all directions of gaze with an inability to raise his eyes above the horizontal midline. Upgaze could not be evoked, and on attempted upgaze he showed convergence movements. Dilated refraction revealed hyperopia of +0.25 sph with astigmatism of −1.0cyl /125° in the right eye and +1.50 hyperopia and −3.5 /175° astigmatism in the left eye. Visual acuity was 0.16 in both eyes. Fundus examination was normal. EOG showed latent nystagmus, and conver-

gent eye movements. Craniocerebral CT scan revealed symmetrical expansion of the ventricular system (mainly third and fourth ventricles) with enlargement of the subarachnoid area and pachygyria. It showed a wedge-shaped hypodense lesion reaching from the right lateral ventricle to the cortex possibly consistent with an infarct in the middle cerebral artery territory or with a porencephalic cyst. The traction test was positive for restriction in all directions. Surgery of the medial and inferior rectus muscles was performed to correct the abnormal head position and revealed stiff and thin-appearing muscle. After disinsertion from the globe the forced duction test was relieved. Muscle biopsy showed replacement of muscle tissue by collagen fibrils, consistent with fibrosis syndrome.

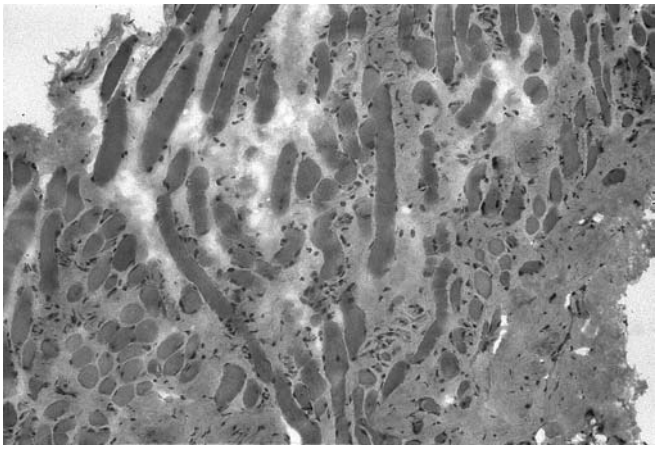

Fig. 4 Patient 4. Haematoxylin–eosin preparation of muscle biopsy specimens of patient 4 reveals extensive endomysial fibrosis of the muscle fibres

Patient 4

An 8 year-old boy born by caesarean section 3 weeks before term presented with a history of neonatal asphyxia, occipital encephalocele and hydrancephaly. He had psychomotor retardation and epilepsy. Ophthalmological examination revealed bilateral ptosis, chin-up head position, exotropia on fixed downgaze and no vertical eye motility. Convergent eye movements could be observed on attempted upgaze. Cycloplegic refraction showed an astigmatism of +1.0 /20° in the right eye and hyperopia of +0.5 with astigmatism of +1.25 cyl /160° in the left eye. Visual acuity was 0.16 in both eyes. Fundoscopy revealed pale optic discs. MRI examination showed the presence of residual temporal and partial frontal brain. During recession of both inferior rectus muscles to correct the chin-up position the traction test confirmed restricted abduction and upgaze. Muscle biopsy revealed extensive endomysial fibrosis of the muscle fibres with varying diameters (Fig. 4).

Genetic analysis

Patients 1 and 2 are brothers, which makes it possible to study linkage of their phenotype to the *FEOM* loci. Seven members of their family, including the two patients and the older brother, parents, maternal grandmother, and maternal uncle, participated in the linkage study (Fig. 5). Given this family's structure, it is possible that the two brothers and their uncle have inherited either an autosomal dominant mutation with reduced penetrance and variable expressivity or an X-linked mutation. Alternatively, the uncle's ptosis could be incidental and the two boys have inherited an autosomal recessive mutation or an autosomal dominant mutation with reduced penetrance. Clinical examination of the parents, grand-

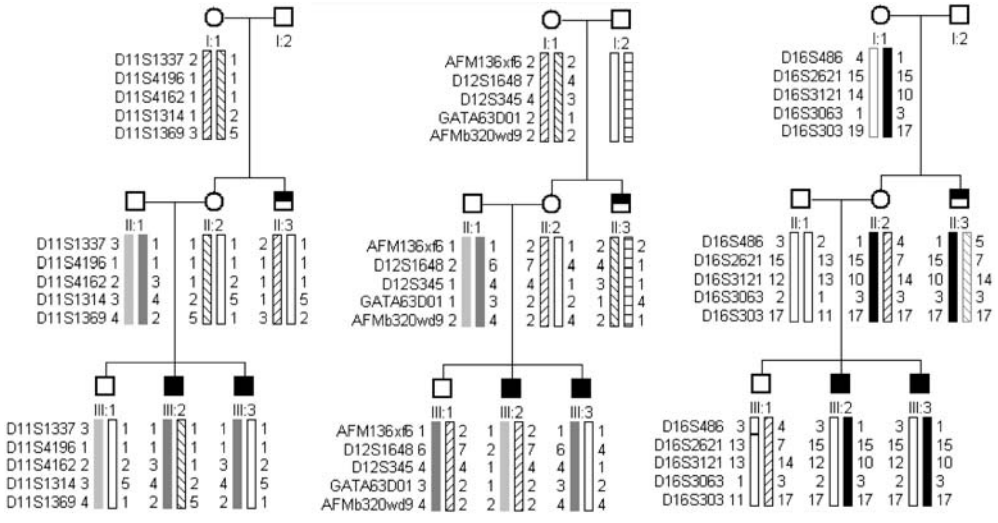

Fig. 5 Haplotype analysis for the pedigree of patients 1 and 2 at the (*left*) *FEOM2* locus on chromosome 11, (*centre*) *FEOM1* locus on chromosome 12 and (*right*) *FEOM3* locus on chromosome 16. *Black symbols* denote those individuals with CFEOM and CNS malformations. *Half-filled symbol* denotes the individual with ptosis. Genotyping data and schematic segregating haplotype bars for polymorphic markers at each critical region are shown below the symbol for each study participant

parents and an older brother showed that all of them had normal vision, full eye motility and no ptosis. Although the family contains too few participants to establish linkage to a specific genetic locus, haplotype analysis of the family using markers that span each *FEOM* critical region can either exclude linkage or be consistent with linkage to a specific locus.

Taking into consideration these various models, the CFEOM phenotype in this family is not co-inherited with either the *FEOM1* or *FEOM2* loci, excluding linkage to these loci based on lod score and haplotype analysis. At the *FEOM1* locus, the affected boys do not share any parental haplotypes and the maternal uncle with ptosis does not share any haplotypes with either boy. At the autosomal recessive *FEOM2* locus, the boys share the same paternal, but not maternal, haplotype. The uncle with ptosis shares neither haplotype.

Analysis of the *FEOM3* locus in this family is consistent with autosomal dominant inheritance with reduced penetrance and variable expressivity. This is the inheritance pattern reported in the first published CFEOM3 family [6]. The two affected boys, their possibly affected maternal uncle, and their unaffected mother and maternal grandmother all inherit a common haplotype across the *FEOM3* region (Fig. 5). Given the small family size, the maximum lod score is only 0.56 at a theta value of zero, assuming the maternal uncle is affected, 90% penetrance, and autosomal dominant inheritance. Therefore, although the data is consistent with linkage to the *FEOM3* locus, this inheritance pattern may have occurred by chance. Of note, loss of a parental allele was not observed in either patient 1 or 2 at any of the *FEOM* loci, suggesting that a contiguous gene deletion syndrome encompassing one of the *FEOM* loci is unlikely.

Discussion

We describe four boys from three unrelated families, all of whom have CFEOM, developmental delay, and neuroimaging findings that reveal central nervous system malformations. The CFEOM phenotype in two of the four boys (patients 1, 4) is "classic"—each has bilateral ophthalmoplegia and ptosis, with the eyes fixed in downgaze and an inability to raise either eye above the horizontal midline. Patients 2 and 3 are not classic because they have unilateral and absent ptosis, respectively. Examination of the biopsied inferior rectus muscles revealed connective tissue and some residual myofibres. The retention of limited eye movements in some of our patients and the presence of residual myofibres in inferior rectus muscles suggest that extraocular muscle function is not completely lost, but in agreement to previous studies replacement of myofibres by fibrous connective tissue and collagen is shown [3]. Although this finding may reflect pathological fibrosis, it may also result from unintentional biopsy of the tendon to muscle transition zone [6].

The CFEOM phenotype found in patients 1 and 2 most closely resembles CFEOM3. Families with CFEOM3 may demonstrate reduced penetrance and variable expressivity. Therefore, it is unclear whether the uncle's apparent ptosis with no evidence of additional CNS maldevelopment results from variable expressivity of a mutation he shares with his nephews or whether the ptosis results from an unrelated process. Genetic analysis of the family reveals that their phenotype is consistent with linkage to *FEOM3* but not to *FEOM1* or *FEOM2*. Therefore, although the family is small and co-inheritance of the phenotype and *FEOM3* could have occurred by chance, the patients will be screened for mutations in the *FEOM3* disease gene once it has been identified. Of note, there have been no previous reports of additional CNS maldevelopment occurring in affected members of *FEOM3*-linked CFEOM families. Patients 3 and 4 present with sporadic disorders that could result from either de novo mutations, recessive disorders, or non-genetic causes.

All four boys have aberrant residual eye movements with synergistic convergence or divergence, and the two brothers have the Marcus Gunn jaw-winking phenomenon. There have been reports of synergistic convergence and divergence in CFEOM1 and unclassified CFEOM families [6, 13], suggesting aberrant innervation of the EOMs. Marcus Gunn jaw winking has been reported in four sporadic cases of CFEOM [13, 19] but, to the best of our knowledge, this is the first report of this association in familial CFEOM. The Marcus Gunn phenomenon has been attributed to aberrant innervation of the levator muscle by a misdirected branch of the fifth cranial nerve [20]. Therefore, these findings also support the concept that aberrant innervation of the extraocular muscles plays a role in the pathology of CFEOM and suggest a primary neurogenic mechanism. Although the aetiology of the Marcus Gunn phenomenon is unknown, reports of three families segregating it as an isolated finding suggests a primary genetic aetiology, at least in some cases [21, 22, 23]. The occurrence of Marcus Gunn jaw winking and CFEOM in siblings, as in our patients 1 and 2, suggests either a primary genetic mechanism or aberrant innervation that has occurred secondary to genetic errors in the development of the oculomotor nucleus. The three familial cases of Marcus Gunn phenomenon and our two siblings with Marcus Gunn phenomenon, cerebral malformation and CFEOM may be consistent with incomplete autosomal hereditary pattern with varied expressivity.

Unlike the majority of reported individuals with CFEOM, whose disorder is limited to the EOM lower motor neuron unit, our patients all have associated anomalies of their cerebellum and/or cerebral cortex. In patients 1 and 2 the brain changes were very similar,

showing agenesis of the corpus callosum, vermis hypoplasia, colpocephaly and abnormal configuration of the pons and the tectum. It is most likely that these cases are genetic. In contrast, in patients 3 and 4, who were sporadic cases, more severe brain changes including pachygyria, expansion of the ventricular system, encephalocele and hydrancephaly were seen. These are anomalies that can result from an early first trimester genetic or environmental insult. The oculomotor nuclei and EOMs develop and migrate during the first trimester as well. Therefore, either a genetic mutation or a first trimester environmental insult could potentially result in the combination of CFEOM and the other CNS abnormalities in patients 3 and 4. If in all four of the patients the disorders are of genetic origin, they may reflect different genetic aetiologies. Although this association lends support to a neurogenic aetiology for CFEOM, common mechanisms can also cause both congenital muscle and brain abnormalities. For example, in certain types of generalised congenital muscular dystrophies, such as the Fukuyama type, the muscle disease is associated with micropolygyria and other brain malformations [24].

There are similarities between the patients in this study and patients reported with Joubert's syndrome. The diagnostic criteria of Joubert's syndrome include vermis hypoplasia, hypotonia, developmental delay and one or both of abnormal breathing and abnormal eye movements [25]. The eye movements are typically described as irregular jerky [26] or as oscillatory [27]. Similar eye movements, corresponding to convergent eye movements rather than nystagmus, have also been described in patients with CFEOM without Joubert's syndrome. Interestingly, there have also been two reports of children who, like patients 1 and 2, meet criteria for both Joubert's syndrome and CFEOM [14, 15]. Moreover, similar to our patients, cases of Joubert's syndrome without CFEOM but with severe psychomotor retardation, meningoencephalocele, dysgenesis of the corpus callosum and abnormalities of the medulla have been described [28, 29, 30, 31]. Autosomal recessive inheritance, which is postulated in Joubert's syndrome [25], is also possible in our patients [1].

In conclusion, we present four additional cases of CFEOM in association with CNS malformations showing that CFEOM can be part of a more complex neurological dysfunction. CNS abnormalities of our patients had similarities to patients with Joubert's syndrome. Two brothers had Marcus Gunn jaw winking in combination with CFEOM and evidence of more diffuse CNS maldevelopment. Aberrant innervation supports primary developmental abnormality of cranial nerves in CFEOM. To the best of our knowledge we describe the first siblings with both CFEOM and Marcus Gunn jaw winking.

Acknowledgements Supported by the Swiss National Science Foundation (no. 32-52503.97), National Institutes of Health R01 EY12498 and EY13583, Deutsche Gesellschaft für Muskelkranke and MAIFOR Programme and by the OPOS Foundation.

References

1. Crawford JS (1970) Congenital fibrosis syndrome. Can J Ophthalmol 5:331–336
2. Heuk G (1879) Ueber angeborenen vererbten Beweglichkeitsdefekt der Augen. Klin Monatsbl Augenheilkd 17:253–278
3. Harley RD, Rodrigues MM, Crawford JS (1978) Congenital fibrosis of the extraocular muscles. Trans Am Ophthalmol Soc 26:198–226
4. Engle EC, Kunkel LM, Specht LA, Beggs AH (1994) Mapping a gene for congenital fibrosis of the extraocular muscles to the centromeric region of chromosome 12. Nat Genet 7:69–73
5. Engle EC, Marondel I, Houtman WA, de Vries B, Loewenstein A, Lazar M, Ward DC, Kucherlapati R, Beggs AH (1995) Congenital fibrosis of the extraocular muscles (autosomal dominant congenital external ophthalmoplegia): Genetic homogeneity, linkage refinement, and physical mapping on chromosome 12. Am J Hum Genet 57:1086–1094
6. Engle EC, Goumernov B, McKeown CA, et al (1997) Oculomotor nerve and muscle abnormalities in congenital fibrosis of the extraocular muscles. Ann Neurol 41:314–325
7. Wang SM, Zwaan J, Mullaney PB, Jabak MH, Al-Awad A, Beggs AH, Engle EC (1998) Congenital fibrosis of the extraocular muscles type 2, an inherited exotropic strabismus fixus, maps to distal 11q13. Am J Hum Genet 63:517–525
8. Nakano M, Yamada K, Fain J, Sener EC et al (2001) Homozygous mutations in ARIX (PHOXA) result in congenital fibrosis of the extraocular muscles type 2. Nat Genet 29:315–320
9. Pattyn A, Morin X, Cremer H, Goridis C, Brunet JF (1997) Expression and interactions of the two closely related homeobox genes Phox2a and Phox2b during neurogenesis. Development 124:4065–4075
10. Guo S, Brush J, Teraoka H, Goddard A, Wilson SW, Mullins MC, Rosenthal A (1999) Development of noradrenergic neurons in the zebrafish hindbrain requires BMP, FGF8, and the homeodomain protein soulless/Phox2a. Neuron 24:555–566
11. Doherty EJ, Macy ME, Wang SM, Dykeman CP, Melanson MT, et al (1999) CFEOM3: A new extraocular congenital fibrosis syndrome that maps to 16q24.2-q24.3. Invest Ophthalmol Vis Sci 40:687–694
12. Abeloos MC, Cordonnier M, Van Nechel C, Van Bogaert P, Gerard JM, Van Regemoorter N (1990) Congenital fibrosis of the ocular muscles: a diagnosis for several clinical pictures. Bull Soc Belge Ophtalmol 24:61–74
13. Brodsky MC (1998) Hereditary external ophthalmoplegia, synergistic divergence, jaw winking, and oculocutaneous hypopigmentation. Ophthalmology 105:717–725
14. Appleton RE, Chitayat D, Jan JE, Kennedy R, Hall JG (1989) Joubert's Syndrome associated with congenital ocular fibrosis and histidinemia. Arch Neurol 46:579–582
15. Jacobson DM, Johnson R, Frens DB (1992) Joubert's syndrome, ocular fibrosis, and normal histidine levels. Am J Ophthalmol 113:714–716

16. Flaherty M, Grattan-Smith P, Steinberg A, Jamieson R, Engle E (2001) Congenital fibrosis of the extraocular muscles associated with cortical dysplasia and maldevelopment of the basal ganglia. Ophthalmology 108:1313–1322
17. Gottlob I, Jain S, Engle EC (2002) Elevation of one eye during tooth brushing. Am J Ophthalmol 134:459–460
18. Brigell M, Bach M, Barber C, Kawasaki K, Kooijman A (1998) Guidelines for calibration of stimulus and recording parameters used in clinical electrophysiology of vision. Calibration Standard Committee of the International Society for Clinical Electrophysiology of Vision (ISCEV). Doc Ophthalmol 95:1–14
19. Brodsky MC, Pollock SC, Buckley DG (1989) Neural misdirection in congenital ocular fibrosis Syndrome: implications and pathogenesis. J Pediatr Ophthalmol Strabismus 26:159–161
20. Pratt SG, Beyer CK, Johnson CC (1984) The Marcus Gunn phenomenon: A review of 71 cases. Ophthalmology 90:27–30
21. Beyer-Machule CK, Johnson CC, Pratt SG, et al (1985) The Marcus-Gunn phenomenon. Orbit 4:15
22. Mrabet A, Oueslati S, Gazzah H, Ben Hamida M (1991) Clinical and electrophysiological study of 2 familial cases of Marcus Gunn phenomenon. Rev Neurol 147:215–219
23. Kirkham TH (1969) Familial Marcus Gunn phenomenon. Br J Ophthalmol 53:282–283
24. Leyten QH, Gabreels FJ, Renier WO, ter Laak HJ (1996) Congenital muscle dystrophy: a review of the literature. Clin Neurol Neurosurg 98:267–280
25. Saraiva JM, Baraitser M (1992) Joubert syndrome: a review. Am J Med Genet 43:726–731
26. Joubert M, Eisenring JJ, Robb JP, Andermann F (1969) Familial agenesis of the cerebellar vermis. A syndrome of episodic hyperpnea, abnormal eye movements, ataxia, and retardation. Neurology 19:813–825
27. Lambert SR, Kriss A, Gresty M, Benton S, Taylor D (1989) Joubert syndrome. Arch Ophthalmol 107:624–631
28. Dekaban AS (1969) Hereditary syndrome of congenital retinal blindness (Leber), polycystic kidneys and maldevelopment of the brain. Am J Ophthalmol 68:1029–1036
29. Jeret JS, Serur D, Wisniewski KE, Lubin RA (1987) Clinicopathological findings associated with agenesis of the corpus callosum. Brain Dev 9:255–264
30. Calogero JA (1977) Vermian agenesis and unsegmented midbrain tectum. Case report. J Neurosurg 47:605–608
31. Suzuki H, Nakazoto A, Ikota H, et al (1983) A case of Joubert syndrome: CT findings of brain stem and review of literature. Brain Dev 15:67–73