

# Cerebellar Atrophy in Congenital Fibrosis of the Extraocular Muscles Type 1

Roberto Di Fabio · Giovanna Comanducci ·  
Francesca Piccolo · Filippo Maria Santorelli ·  
Teresa De Berardinis · Alessandra Tessa ·  
Umberto Sabatini · Francesco Pierelli · Carlo Casali

© Springer Science+Business Media, LLC 2012

## Introduction

Congenital fibrosis of the extraocular muscle (CFEOM) syndromes are hereditary eye movement disorders characterized by restrictive paralytic ophthalmoparesis with or without ptosis [1]. Typically, pupillary function, anterior segment examination, and fundus oculi are normal.

CFEOM type 1 (MIM 608283) is an autosomal dominant disorder, which maps to chromosome 12q12 and presents

the classical paralytic ophthalmoparesis phenotype [2]. Neuropathology has revealed absence of the superior division of the oculomotor nerve and its corresponding  $\alpha$ -motoneurons in the midbrain, associated with dysplasia of the levator palpebrae superioris and the superior rectus muscles [1, 3]. Most CFEOM1 individuals harbor heterozygous mutations in the developmental kinesin gene, *KIF21A* [4].

CFEOM2 (MIM 602753) is an autosomal recessive form of the disease, clinically consisting of exotropic ophthalmoparesis and ptosis, and mapping to chromosome 11q13 in Saudi Arabian and Turkish families [5]. A further variant (CFEOM3) is multifaceted and can be associated with dominant mutations in *TUBB3* (CFEOM3A, MIM 600638) if combines ptosis and restrictive external ophthalmoparesis [6, 7]. Bilateral or unilateral manifestations are possible, and penetrance can be incomplete. Individuals may be able to raise the eyes above midline or may not have blepharoptosis [8]. Instead, CFEOM3B (MIM 135700) was reported in a Turkish family carrying a mutation in *KIF21A*, and it is clinically different from CFEOM1 because the absence of ptosis, unilateral ophthalmoparesis, non-infraducted primary eye position, or the ability to raise at least one globe above the horizontal midline were all observed in at least one family member [4, 9]. Finally, CFEOM3C (MIM 609384) was described in a single patient carrying a balanced/unbalanced reciprocal translocation  $t(2;13)(q37.3;q12.11)$  who presented CFEOM in association with mental retardation and facial dysmorphism [10].

Additional extraocular signs can occasionally occur in CFEOM, such as in the Tukel syndrome, a rare disorder in which ophthalmoparesis and ptosis are accompanied by oligodactyly–syndactyly of the hands [11]. Cerebellar involvement has been observed in patients having mutations in *TUBB3*, though in the context of a more severe and widespread abnormal cortical neurodevelopment disorder

**Electronic supplementary material** The online version of this article (doi:10.1007/s12311-012-0396-0) contains supplementary material, which is available to authorized users.

R. Di Fabio (✉) · F. Piccolo · F. Pierelli · C. Casali  
Department of Medical–Surgical Science and Biotechnology,  
Sapienza University of Rome,  
Corso della Repubblica, 79,  
04100 Latina, Italy  
e-mail: rodifa@gmail.com

G. Comanducci  
Department of Neurology, San Camillo Hospital,  
Rome, Italy

F. M. Santorelli · A. Tessa  
Molecular Medicine & Neurodegenerative Diseases, IRCCS  
Fondazione Stella Maris,  
Pisa, Italy

T. De Berardinis  
Department of Ophthalmological Sciences, University of Naples,  
Naples, Italy

U. Sabatini  
Department of Radiology, IRCCS Santa Lucia,  
Rome, Italy

F. Pierelli  
IRCCS Neuromed,  
Pozzilli, Italy

[12]. Herein, we describe two patients from CFEOM1 kindred who showed cerebellar atrophy on neuroimaging and, in adulthood, developed a slowly progressive ataxia, affecting gait and balance.

## Patients and Methods

The family (Fig. 1) has already been described elsewhere. It is the CZ pedigree in [2] in association with the heterozygous p.R954W mutation in *KIF21A* in several individuals with nearly full penetrance [2].

The proband (I-1) is a 79-year-old man who presented, on clinical examination, severe congenital bilateral ptosis and ophthalmoparesis characterized by inability to raise his eyes above the horizontal midline and very limited lateral eye movements. He had undergone surgery in adulthood. In his 50s, he started experiencing balance problems. No segmental ataxia was evident, but the patient's gait was broad-based and tandem walking was impossible. In addition, the patient was severely dysarthric. The MRI examination revealed a marked cerebellar atrophy, both in the cerebellar hemispheres and in the vermis, a homogeneous signal intensity of the cerebral parenchyma, any focal abnormalities, in either the gray or white matter. The cortex was of normal thickness and had regular sulcation. The ventricular system showed a moderate increased size, symmetrical at the midline. The sub-arachnoid spaces were regular, in agreement with patient's age. On the whole, the MRI examination presents subtentorial atrophy (Figs. 2a and 3).

Patient II-1 is a 53-year-old woman who has developed gait difficulties in the past 2 years. On neurological examination, she showed significant ptosis and ophthalmoparesis, involving up and downgaze mainly, but also horizontal eye

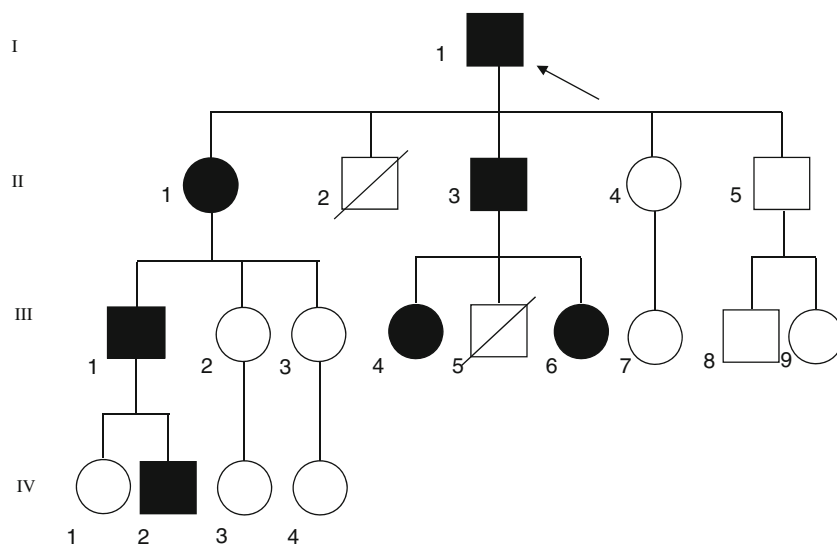
movements to a lesser extent. She showed mild difficulty with tandem gait. Her MRI examination showed slight enlargement of the fourth ventricle and of the cerebellar sub-arachnoid spaces, prominent posterior fossa sub-arachnoid cisterns, suggesting an initial cerebellar atrophy (Fig. 2b).

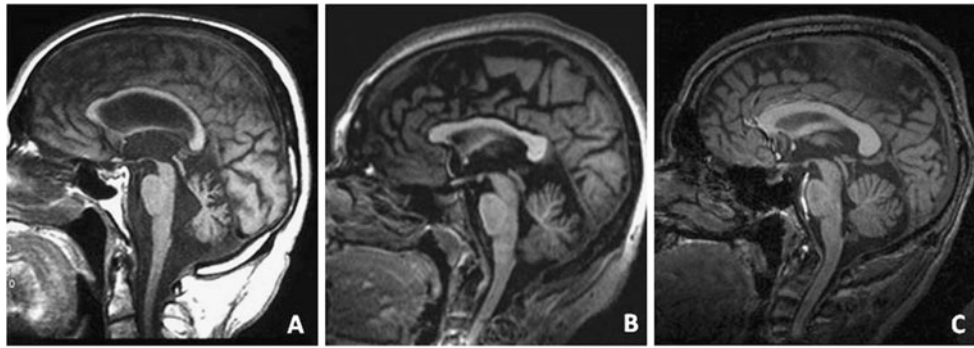
Her 50-year-old brother (II-3) also started presenting moderate gait abnormalities over the last few years but refused further neuroimaging examination. Patient III-4 is a 33-year-old woman affected by congenital bilateral ptosis and ophthalmoparesis. Her neurological examination and brain neuroimaging findings were normal (Fig. 2c).

## Discussion

Congenital bilateral ptosis and non-progressive restrictive ophthalmoparesis are the pivotal signs of CFEOM, which can be inherited as an autosomal dominant (CFEOM1 and CFEOM3) [2, 4, 6] or autosomal recessive (CFEOM2) [5] trait. In addition to bilateral ptosis and restrictive external ophthalmoparesis with the eyes partially or completely fixed in infraducted and strabismic position, extraocular signs are also possible, including oligodactyly–syndactyly of the hands [11], mental retardation and facial dysmorphism [10], and Marcus Gunn jaw winking phenomenon and epilepsy [13]. Patients with the latter variant can also show neuroradiological abnormalities, such as agenesis of the corpus callosum, colpocephaly, and enlarged ventricles, or widespread cortical dysplasia and caudate hypoplasia [14]. To date, however, no patient with genetically confirmed CFEOM1 has manifested clinical symptoms of cerebellar atrophy. In a study by Yoshida and co-workers [15], direct gene testing failed to detect alterations in *KIF21A* in several members of a Japanese pedigree with syndromic CFEOM. Interestingly, cerebellar hypoplasia,

**Fig. 1** A family with congenital fibrosis of the extraocular muscles type 1





**Fig. 2** MRI T1-weighted brain sagittal scans showing three patients (a–c) affected by congenital fibrosis of the extraocular muscles type 1. **a** (patient I-1 in the pedigree): marked atrophy of the cerebellum, both in the cerebellar hemispheres and in the vermis. **b** (patient II-1):

enlargement of the fourth ventricle and cerebellar sub-arachnoid spaces, prominent posterior fossa sub-arachnoid cisterns, indicating initial cerebellar atrophy. **c** (patient III-4): normal morphology, size, and signal intensity of the cerebellum

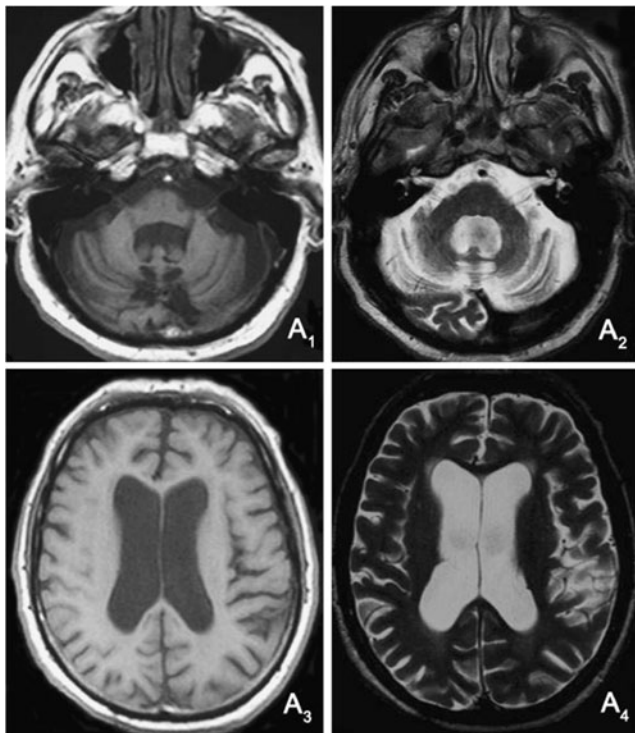
more prominent in the vermis than in the hemispheres, was seen in all the family members, although only middle-aged subjects showed signs of gait ataxia, which had appeared in adolescence. However, the disorder appeared to exhibit incomplete penetrance since two younger family members with CFEOM showed no clinical signs of cerebellar involvement.

We observed cerebellar vermis atrophy and late-onset cerebellar syndrome in two patients harboring the p.R954W mutation in *KIF21A*. No signs or symptoms other than

CFEOM were seen in patient III-4, the 33-year-old daughter of case II-1, who also had an unremarkable brain MRI.

Most patients with CFEOM1, and rare cases of CFEOM3, harbor mutations in the kinesin gene *KIF21A*, whose exact function is unknown [2]. Kinesins transfer cargo along microtubules and are responsible for anterograde axonal transport in neurons. In mammalian cells, kinesins are tetrameric proteins containing two heavy (alpha) chains, which provide the tubulin binding site and the ATPase domains, and two light (beta) chains, which are responsible for kinesin specificity for organelle binding [16]. It has been suggested that *KIF21A* mutations could interfere with protein dimerization [17]. During embryonic life, this impairment could lead to deficient cargo transport from the oculomotor motoneurons to the developing neuromuscular junction of the extraocular muscle, resulting in hypotrophy of these muscles at birth. It is tempting to hypothesize that failure of kinesin-dependent neuronal transport could also be responsible for the anatomical malformation of the cerebellum observed in some subjects. Consistent with this idea is the recent finding that kinesin light-chain KLC3 [18] is highly expressed in the adult cerebellum. Accordingly, a marked decrease in the density of synaptic vesicles and in the amount of synaptic terminals, as well as a focal neuronal loss in several brain areas of *KIF1A* motor protein-deficient mice, has been observed. Moreover, the premature neuronal death matches chronologically with the beginning of production of *KIF1A* in wild-type cells, this supporting the hypothesis that the reduction of kinesin transport in mutated neurons may be crucial for keeping cellular trophism [19].

Since we observed a cerebellar syndrome and subtentorial hypotrophy only in the two older patients with CFEOM1, but not in a younger relative, we cannot exclude that impaired cargo transport could cause gradual cerebellar atrophy, mainly of the vermis, with aging. Establishing the exact time frame of this mechanism in CFEOM1, however, is a difficult task that will require clinical and radiological follow-up.



**Fig. 3** Axial brain MRI in a 79-year-old patient with congenital fibrosis of extraocular muscles (I-1 in the pedigree). T1 (A1) and T2-weighted (A2) scans at the level of fourth ventricle. T1 (A3) and T2-weighted (A4) images at the level of corona radiata

## Summary

We described a family with a molecularly confirmed form of CFEOM1 and a late-onset cerebellar syndrome. Brain MRI showed vermis atrophy in two older family members, who also manifested gait impairment, whereas both neurological examination and neuroimaging findings were normal in a younger relative who harbored the same mutation.

Although clinical and radiological follow-up of patients are needed to confirm the existence of a close link between a kinesin motor protein and the development of cerebellar atrophy, we propose to investigate *KIF21A* in autosomal dominant, late-onset, ataxic syndromes with progressive oculomotor impairment and ptosis. Conversely, signs of cerebellar involvement should be assessed in adult CFEOM1 patients.

**Conflict of Interest** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## References

- Engle EC, Goumernov B, McKeown CA, Schatz M, Johns DR, Porter JD, et al. Oculomotor nerve and muscle abnormalities in congenital fibrosis of the extraocular muscles. *Ann Neurol*. 1997;41(3):314–25.
- Yamada K, Andrews C, Chan WM, et al. Heterozygous mutations of the kinesin KIF21A in congenital fibrosis of the extraocular muscles type 1 (CFEOM1). *Nat Genet*. 2003;35(4):318–21.
- Demer JL, Clark RA, Engle EC. Magnetic resonance imaging evidence for widespread orbital dysinnervation in congenital fibrosis of extraocular muscles due to mutations in KIF21A. *Invest Ophthalmol Vis Sci*. 2005;46(2):530–9.
- Yamada K, Chan WM, Andrews C, et al. Identification of KIF21A mutations as a rare cause of congenital fibrosis of the extraocular muscles type 3 (CFEOM3). *Invest Ophthalmol Vis Sci*. 2004;45(7):2218–23.
- Nakano M, Yamada K, Fain J, Sener EC, Selleck CJ, Awad AH, et al. Homozygous mutations in ARIX(PHOX2A) result in congenital fibrosis of the extraocular muscles type 2. *Nat Genet*. 2001;29(3):315–20.
- Doherty EJ, Macy ME, Wang SM, Dykeman CP, Melanson MT, Engle EC. CFEOM3: a new extraocular congenital fibrosis syndrome that maps to 16q24.2–q24.3. *Invest Ophthalmol Vis Sci*. 1999;40(8):1687–94.
- Tischfield MA, Baris HN, Wu C, et al. Human TUBB3 mutations perturb microtubule dynamics, kinesin interactions, and axon guidance. *Cell*. 2010;140(1):74–87.
- Heidary G, Engle EC, Hunter DG. Congenital fibrosis of the extraocular muscles. *Semin Ophthalmol*. 2008;23(1):3–8.
- Sener EC, Lee BA, Turgut B, Akarsu AN, Engle EC. A clinically variant fibrosis syndrome in a Turkish family maps to the CFEOM1 locus on chromosome 12. *Arch Ophthalmol*. 2000;118:1090–7.
- Aubourg P, Krahn M, Bernard R, et al. Assignment of a new congenital fibrosis of extraocular muscles type 3 (CFEOM3) locus, FEOM4, based on a balanced translocation t(2;13)(q37.3;q12.11) and identification of candidate genes. *J Med Genet*. 2005;42(3):253–9.
- Tukel T, Uzumcu A, Gezer A, et al. A new syndrome, congenital extraocular muscle fibrosis with ulnar hand anomalies, maps to chromosome 21qter. *J Med Genet*. 2005;42(5):408–15.
- Poirier K, Saillour Y, Bahi-Buisson N, et al. Mutations in the neuronal  $\beta$ -tubulin subunit TUBB3 result in malformation of cortical development and neuronal migration defects. *Hum Mol Genet*. 2010;19(22):4462–73.
- Pieh C, Goebel HH, Engle EC, Gottlob I. Congenital fibrosis syndrome associated with central nervous system abnormalities. *Graefes Arch Clin Exp Ophthalmol*. 2003;241(7):546–53.
- Flaherty MP, Grattan-Smith P, Steinberg A, Jamieson R, Engle EC. Congenital fibrosis of the extraocular muscles associated with cortical dysplasia and maldevelopment of the basal ganglia. *Ophthalmology*. 2001;108(7):1313–22.
- Yoshida K, Okano T, Hoshi K, et al. Congenital fibrosis of the extraocular muscles (CFEOM) syndrome associated with progressive cerebellar ataxia. *Am J Med Genet A*. 2007;143A(13):1494–501.
- Junco A, Bhullar B, Tarnasky HA, van der Hooft FA. Kinesin light-chain KLC3 expression in testis is restricted to spermatids. *Biol Reprod*. 2001;64(5):1320–30.
- Engle EC. The genetic basis of complex strabismus. *Pediatr Res*. 2006;59(3):343–8.
- Chung S, Zhang Y, Van Der Hooft F, Hawkes R. The anatomy of the cerebellar nuclei in the normal and scrambler mouse as revealed by the expression of the microtubule-associated protein kinesin light chain 3. *Brain Res*. 2007;1140:120–31.
- Yonekawa Y, Harada A, Okada Y, et al. Defect in synaptic vesicle precursor transport and neuronal cell death in KIF1A motor protein-deficient mice. *J Cell Biol*. 1998;141:431–41.