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Congenital Fibrosis of Extraocular Muscles Type 1 with Progression of Ophthalmoplegia

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Abstract
Background: Congenital fibrosis of the extraocular muscles type 1 (CFEOM1) is a congenital, non-progressive autosomal-dominant disorder with bilateral oculomotor nerve palsy due to mutations in the kinesin motor protein gene KIF21A.
Results: We present a 60-year old patient with CFEOM1 due to the common C2860T mutation in KIF21A. At the age of 37, he complained about newly occurred diplopia, which implies the capability of binocular vision before. The divergence of both globes progressed and the poor residual movement on attempted adduction and upgaze completely disappeared during the sixths decade. Clinical and electromyographic examination showed isolated involvement of the oculomotor nerve.
Conclusion: Apparently, progression of impaired ocular motility is not contradictory to the diagnosis of this congenital developmental disorder. Mechanical, contracture-like mechanisms as known from other types of strabism or persistent overuse of the reduced number of oculomotor α-motoneurons are generally considered as a reason for clinical progression. However, regarding the underlying known molecular basis of CFEOM1, a continuous disease progression due to the kinesin dysfunction cannot be excluded.

Key words: Congenital fibrosis, extraocular muscles type 1 (CFEOM1), dysinnervation disorders (CCDD), kinesin motor protein gene KIF21A

Introduction

The newly-classified congenital cranial dysinnervation disorders (CCDD) are defined as congenital, non-progressive, sporadic or familial developmental abnormalities of the cranial nerves [4, 6]. The different phenotypes of CCDD include the congenital fibrosis of extraocular muscles (CFEOM type 1-3), congenital ptosis, Duane syndrome, horizontal gaze palsy, Möbius syndrome, and congenital facial palsy.

CFEOM 1 (MIM 135700), the most common type of the three CFEOM phenotypes, is clinically characterized by (a) a congenital non-progressive bilateral ptosis and ocular motility disorder (b) with infraducted globes in primary position (c) restricted upgaze and variably restricted horizontal gaze, (d) positive forced duction test, (e) variable occurrence of aberrant eye movements and (f) autosomal-dominant inheritance with high penetrance [2, 3].

Recently, mutations responsible for CFEOM1 in the KIF21A gene on chromosome 12p11.2 q12 were identified [2]. These heterozygous mutations in the kinesin motor protein gene might lead to disrupted axonal transport resulting in impaired development of the superior division of the oculomotor nerve and its corresponding midbrain nuclei [3, 10].

We present a case of CFEOM1 that was previously shown to harbor a mutation in KIF21A [6, 10], and provide additional data supporting progression of his external oculomotor nerve palsy.

Case Report

The patient attended the clinic for the first time at the age of 37. At that time he was found to experience diplopia and increasing blurred vision by eye lashes. This implies that previously he was capable of fusing and had binocular vision. Due to the progression of ocular symptoms, he had to give up his profession as a cabinet-maker at the age of 35. He had always refused an operation.

Both bulbi were in down gaze with hypotropia of the left side. He had bilateral ptosis, pronounced on the left side. Attempted upgaze led to bilateral adduction with jerky movements. There was myopia and astigmatism on both eyes. Visual acuity was cc 20/40 OD (right eye) and 20/32 OS (left eye). Pupillary findings, slit lamp, ocular tension and ophthalmoscopic examination were normal. Visual field borders were normal. Electroretinogramm showed normal scotopic and photopic potentials. Electromyographic examination at the age of 40 revealed a neurogenic pattern in both the right superior and medial rectus muscles.

The ptosis became symmetrical and widths of the palpebral fissure ranged between 2.5 and 1.0 mm between the ages of 45 and 59. The angle of divergence of both bulbi was 26° at the age of 37, 34° at the age of 40 and, 40° at the age of 49. Since the age of 50 both globes were found to be in down gaze with maximal divergent deviation (45°). Poor residual movement on attempted adduction and upgaze had completely

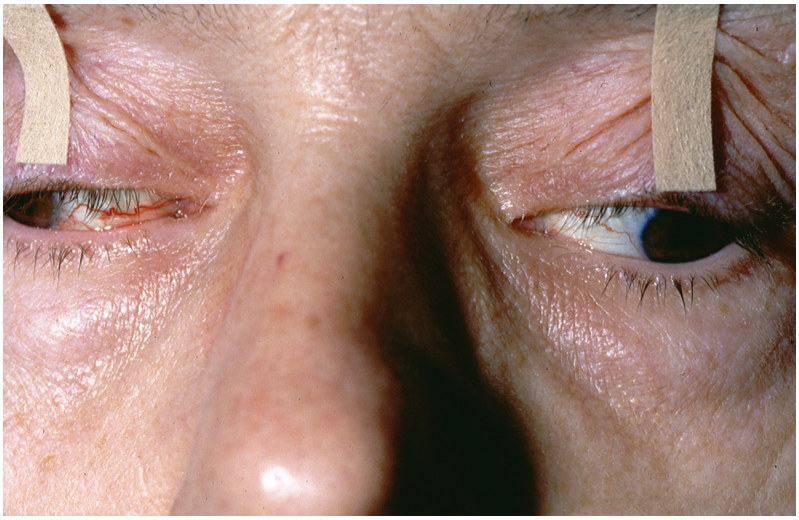

Fig. 1. Index patient at age 54. Bulbi in primary position.

disappeared since the age of 59. Restriction of motility resulted in progressive compensatory frontal innervation and chin-up position with retro- and laterocollis (Fig. 1). Since the fifth decade, walking on uneven grounds, working with raised arms, and car-driving had become difficult.

The neurological examination at the age of 57 revealed no further abnormalities. Laboratory results showed no pathological findings, including CK, lactate, TSH, thyroid gland autoantibodies, anti-acetylcholine receptor antibodies. Edrophonium i. v. test was normal. Muscle biopsy of the biceps muscle revealed no abnormalities including ragged red fibers. Apart from subtle neurogenic changes in two out of four muscles EMG findings were normal. Repetitive stimulation (3/sec) of the facial nerve showed no pathological decrement, single fiber EMG was normal. The motor nerve conduction velocity of both tibial nerves was normal. Brain MRI showed normal configuration of pons and mesencephalon and no further abnormalities.

The patient's sister, his father, the sister of his father and his grandfather were also affected by congenital ptosis and downward strabism.

Molecular studies excluded oculopharyngeal muscular dystrophy and mitochondrial point mutations (A3243G, A8344G) or deletions of mtDNA by Southern blot and long PCR from muscle tissue. Genetical analysis of this patient by Yamada et al revealed a R954W (C2860T) point mutation in exon 21 at the KIF21A gene at chromosom 12p11.2 q12 (patient FD) [10].

Discussion

CFEOM counts per definition for a congenital and non-progressive developmental disorder. The documented course of our patient, however, clearly showed progression of the bilateral external ophthalmoplegia over the last 23 years. Other, possible coincidental disorders causing progredient external ophthalmoplegia could be excluded.

The progressive ptosis might be readily a secondary effect due to fatigue of the frontal muscle caused by the retroflexed head and ageing of the tarsal connective tissue. Progressive impairment of the oculomotor nerve function, however, could reflect either a further contracture or degeneration or the result of an overuse of a reduced number of the other oculomotor brain stem α-motoneurons. Furthermore, mechanical, contracture-like mechanisms as known from other types of strabism should be considered as a reason for clinical progression. For example, patients with Duane syndrome are well recognized to have progressive contracture of the medial rectus muscle and recurrence of esotropia following initial surgeries. Additionally, excessive metabolic stress on the remaining motor neurons over many years could result in exhaustion of a congenitally reduced number of oculomotor α-motor neurons with impaired axonal transport. This could be seen in analogy to mechanisms in the postpolio syndrome, which is characterized by the occurrence of new weakness or muscle atrophy after a period of functional stability of usually > 15 years [1].

The underlying mutations of KIF21A in CFEOM1 possibly result in impaired development of circumscribed oculomotor nuclei populations and its axons. Engle et al. (1997) found decreased motoneuron numbers in the third and fourth nerve and abnormal skeletal muscle biopsies of children with CFEOM [3]. Since the kinesin motor protein KIF21A is involved in anterograde and retrograde axonal transport, a disturbance of KIF21A might lead to further degeneration of the remaining oculomotor α-motoneurons [8]. Examples for impaired axonal transport in progressive motorneuron diseases are a transgenic SOD1 mouse-model [9] and mutations of the dynein motor protein in mice [5]. Animal models of motor neuron disease suggest that motor neuron degeneration clearly precedes the onset of symptoms. Compensatory mechanisms might be successful in maintaining motor functions until a critical number of motor units have been lost [7]. In the present case it cannot be assessed on a merely clinical basis, whether the progression was continuous or started during the fourth decade.

On a clinical point of view the criterion of absent progression in CFEOM1 seems to be questionable.

References

1. Dalakas MC (1995) Pathogenetic mechanisms of Post-Polio Syndrome: Morphological, electrophysiological, virological, and immunological correlations. Ann N Y Acad Sci 753: 167-85
2. Engle EC, Kunkel LM, Specht LA und 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
3. Engle EC, Goumernov B, McKeown CA, Schatz M, Johns DR, Porter JD und Beggs AH (1997) Oculomotor nerve and muscle abnormalities in congenital fibrosis of the extraocular muscles. Ann Neurol 41: 314-25
4. Gutowski NJ, Bosley TM, Engle EC (2003) 110th ENMC International Workshop: The congenital cranial dysinnervation disorders (CCDDs), Naarden, The Netherlands, 25-27 October 2002. Neuromuscular Disorder 13: 573-578
5. Hafezparast M, Klocke R, Ruhrberg C, Marquardt A, Ahmad-Annuar A, Bowen S et al. (2003) Mutations in dynein link motor neuron degeneration to defects in retrograde transport. Science 300: 808-12
6. Hanisch F, Bau V, Zierz S (2005). Congenital fibrosis of extraocular muscles (CFEOM) and other phenotypes of congenital cranial dysinnervation syndromes (CCDD). Nervenarzt 76: 395-402
7. Ludolph AC (2000) Treatment of amyotrophic lateral sclerosis – what is the next step? J Neurol 247 (Suppl 6): 13-18
8. Marszalek JR, Weiner JA, Farlow SJ, Chun J, Goldstein LSB (1999) Novel dendritic kinesin sorting identified by different process targeting of two related kinesins: KIF21A and KIF21B. J Cell Biol 3: 469-79
9. Murakami T, Nagano I, Hayahi T, Manabe Y, Shoji Y, Setoguchi Y, et al. (2001) Impaired retrograde axonal transport of adenovirus-mediated E. coli LacZ gene in the mice carrying mutant SOD1 gene. Neurosci Lett 308: 149-52
10. Yamada K, Andrewa C, Chan W-M, McKeown CA, Magli A, de Berardinis T et al (2003) Heterozygous mutations of the kinesin KIF21A in congenital fibrosis of the extraocular muscles type 1 (CFEOM1). Nature Genetics 35: 318-21

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