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Case report

Early onset facioscapulohumeral muscular dystrophy – Long-term follow-up of a patient with total facial diplegia

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Abstract

We report a patient with early onset facioscapulohumeral muscular dystrophy type 1 (FSHD1) who was not diagnosed until 48 years of age. She developed progressive facial diplegia from the age of 4–5 years followed by limb muscle weakness. Motor nerve conduction was normal, myopathic changes were seen electromyographically. Creatine kinase activity was mildly increased at the beginning. Muscle biopsy at 8 years suggested a neurogenic pattern, a second biopsy at age 30 was chronic myopathic with fibre calibre variation. The patient lost the ability to walk at age 44. When last seen she had total facial diplegia, no active movements in her limbs, mild kyphoscoliosis and a rigid thoracic spine. Molecular studies revealed a shortened D4Z4 fragment confirming the diagnosis FSHD1. Her family history was unremarkable, suggesting a *de novo* mutation. This report is to illustrate the evolving phenotype of early onset FSHD1 with predominating facial palsy.

Keywords: Facioscapulohumeral muscular dystrophy; Early-onset; Low copy D4Z4 repeat; Facial palsy.

1. Introduction

Facioscapulohumeral muscular dystrophy (FSHD) type 1 is a common muscular dystrophy with an estimated prevalence of 1 in 15,000 caused by a heterozygous contraction of D4Z4 repeats on a chromosome with a 4qA haplotype [1]. The classical phenotype includes facial weakness followed sequentially by scapular fixator, humeral, truncal, and lower-extremity weakness. However, the clinical picture is diverse and often atypical including scapular or scapuloperoneal muscular dystrophy, infantile facial diplegia, limb girdle muscular dystrophy, distal or monomelic myopathy and bent spine syndrome. We report on the long-term disease course and the evolving facial phenotype of a patient with very short (2) D4Z4 repeats.

2. Case report

The patient was the only daughter of healthy parents, her younger brother was healthy, and family history was negative regarding neuromuscular disorders. In infancy psychomotor development was normal, and no facial abnormalities were apparent until around age 4 (Fig. 1(a)–(c)). In her 6th year incomplete closure of eyelids and drooling was noted and resulted in first neuropediatric examinations. Initial diagnosis was "incomplete facial paralysis". Two years later at age 8, facial weakness had progressed to absence of facial movements. In addition, the patient had developed shoulder girdle weakness with scapular winging followed by proximal weakness of the lower limbs. At that time distal musculature was considered unaffected. By examination of her skeletal features, pectus carinatum and kyphoscoliosis were documented. Tendon reflexes of lower limbs were reduced, there were no pyramidal signs and no sensory

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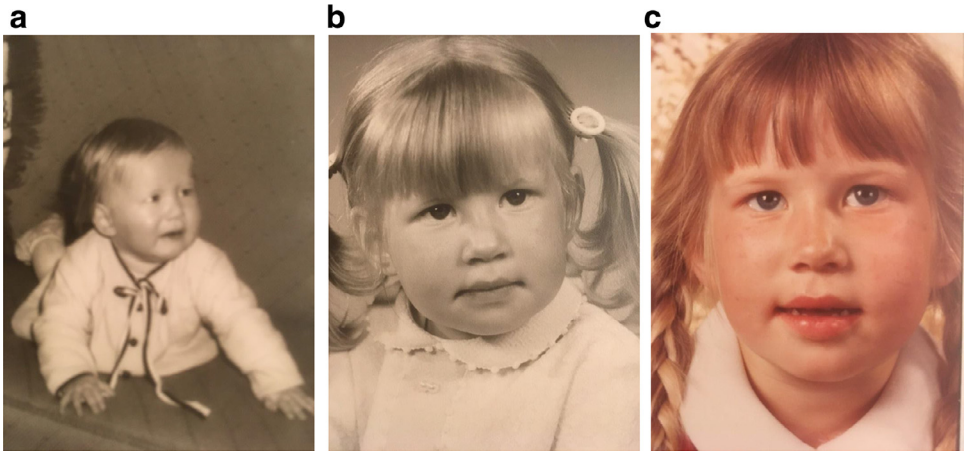

Fig. 1. The patient at different ages prior to disease onset: 7 months (a), 2 years (b). Facial weakness can be assumed at 4 years (c), but was not recognized till 5 years of age.

disturbances, intelligence was above average (IQ 129). CK activity was slightly increased (132 U/l, no normal range provided). First muscle biopsies (1977, University of Zurich, Switzerland) obtained from the deltoid and quadriceps muscles showed an abnormal variation of fibre calibres and groups of atrophic fibres suggesting a neurogenic lesion. Progression of weakness was noted (Fig. 2(a) and (b)), there were no further investigations until age 30. At that time the patient was confined to a wheelchair for outdoor activities, had facial diplegia and marked proximal and distal limb muscle atrophies (MRC grade 4 hip and feet flexors, normal toe extension), atrophic abdominal muscles, and kyphoscoliosis. Tendon reflexes were absent apart from ASR. Laboratory studies revealed a near normal CK activity 75 U/l (normal <50 U/l), normal lactate, but slightly increased transaminases (GOT 17–37 U/l, normal <15 U/l; GPT 25–42 U/l, normal <22 U/l) and gamma GT (89–138 U/l, normal <20 U/l). Electromyographically, a myopathic pattern was seen with reduced amplitudes and polyphasic potentials, whereas motor nerve conduction studies were normal. A further muscle biopsy (peroneal muscle) at

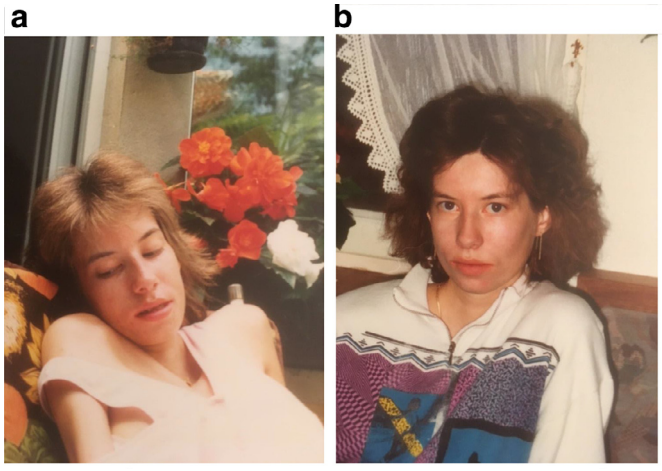

Fig. 2. Facial diplegia and shoulder girdle weakness seen at 15 (a) and 25 (b) years of age.

age 30 (Institute for Neuropathology, University Hospital Aachen, Germany) showed a moderate non-necrotizing, non-inflammatory myopathy with focal accumulations of glycogen

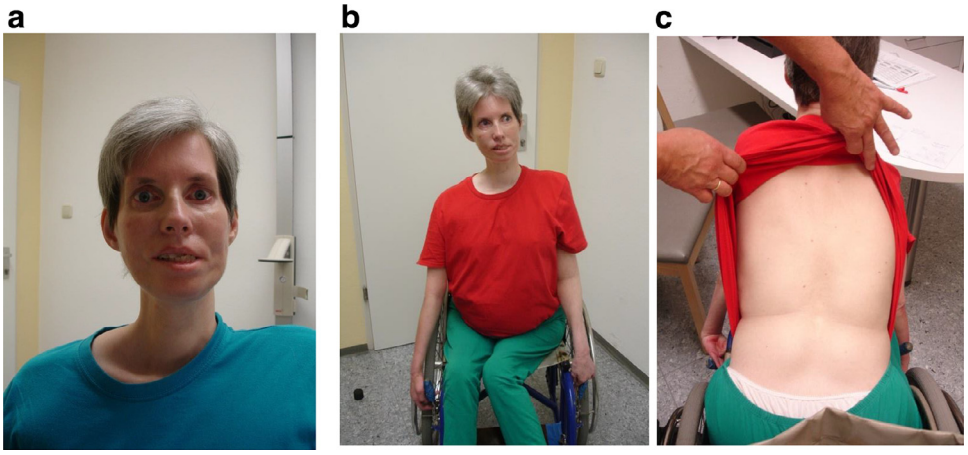

Fig. 3. The 48-year old patient when last examined. No facial movements possible (a), proximal and distal extremity weakness, no antigravity movements possible (b), mild scoliosis and rigid thoracic spine (c).

in several muscle fibers which were thought to be either artificial or indicative of a mild glycogen storage disorder. However, subsequent enzyme histochemical and biochemical workup did not provide any evidence of acid maltase, myophosphorylase, phosphofructokinase or branching enzyme deficiency.

When first seen for genetic consultation at age 48 (Fig. 3(a)–(c)), the patient was non-ambulatory following a tibia fracture at age 44. She had mild scoliosis, her thoracic spine was rather rigid. She was unable to rise her arms or legs against gravity, and no facial movements could be provoked. Molecular diagnosis of FSHD1 was initiated: digestion of genomic DNA with restriction enzymes *EcoRI*, *EcoRI+BlnI* (double digest), Southern blotting and hybridization with the DNA probe p13E11 showed a shortened fragment at the D4Z4 locus of 15 kb (*EcoRI*) reducing to 12 kb on double digest (*EcoRI+BlnI)*. The DNA probe p13E11 recognizes also a homologous repeat array on chromosome 10q26, but which was excluded being the origin of the 15/12 kb fragment by additional XapI digestion. To verify that the obtained shortened D4Z4 fragment on chromosome 4 has a causative 4qA haplotype, an additional Hind III-Southernblot was performed establishing the diagnosis of FSHD1 [2]. There was no evidence of affected relatives. The 85 year old mother was still physically active and caretaker of her daughter. As the father died at age 72 from unrelated reasons (leukemia), no further investigations were undertaken to confirm a *de novo* mutation.

3. Discussion

The clinical picture of our patient challenged the diagnostic work-up for many years. First neurological examinations took place more than 40 years ago, i.e., before molecular confirmation was possible, since the shortened D4Z4 fragment as the main cause of FSHD was first identified in 1992. Molecular genetic analysis for FSHD1 is laborious and based on Southern blots and Southern hybridisation [2]. This is the only tool for the correct diagnosis. It cannot be included in massive parallel sequencing analysis. This means the clinician has to have a specific idea to initiate the right laboratory test.

Early onset FSHD1 is characterized by childhood onset, rapid progression of muscle disease, extra-muscular features, and very short D4Z4 repeats on chromosome 4q35 [3–6]. It affects about 5–10% of FSHD patients and has been clinically defined by signs or symptoms of facial weakness before the age of 5 and signs or symptoms of scapular weakness before the age of 10 [7]. However, despite the large number of published cases, there is no photographic documentation of longterm disease courses. Facial weakness can be so severe that it can be mistaken by as Möbius syndrome, a cranial dysinnervation disorder, characterized by congenital facial paralysis and absence of facial expression, but usually also with deficient eye movement, which is not a feature in FSHD. Congenital facial diplegia has been reported in two sisters born to a mother with classical FSHD1 [8], underlining the clinical variability of FSHD within families.

In an Italian study comprising 114 index cases with short D4Z4 repeats consisting of 1–3 units, facial weakness was reported as the presenting feature in 76.5% [3]. Two patients were misdiagnosed as Möbius syndrome. However, the authors stated that even with an onset in the first year, disease outcome did not differ from later onset cases who also have 1–3 repeat units. Patients with 1–3 units showed a higher proportion of de novo mutations (60.6%) compared with 5.7% in a cohort of patients with 4–8 units [3]. Moreover, 4 patients with somatic mosaicism were identified.

In a systematic review of published patients with early-onset FSHD [4], 227 patients were identified with a mean age at onset of 2.8 years, of whom 25% showed symptoms in the first year of life. The authors found that the pattern of muscle involvement was similar to the classical FSHD phenotype with facial, scapulohumeral, axial and peroneal weakness. Loss of ambulation was recorded in 40% of patients occurring at a mean age of 17 years. Systemic features were reported in 50% of patients and included hearing loss (40%), retinopathy (37%), epilepsy (8%), developmental delay (15%), pulmonary and cardiac abnormalities. Full genetic information was available for 93 families; a *de novo* mutation was found in 73% of patients, 12% were somatic mosaics [4]. Mean D4Z4 repeat length was 14.2 kb with a range of 9–31 kb. A shorter D4Z4 repeat length was associated with a higher age-corrected clinical severity score, more wheelchair dependency, more hearing loss, and more epilepsy [4].

In a multinational cross-sectional study of 52 genetically confirmed FSHD1 patients who had facial weakness before 5 years and/or shoulder girdle weakness before 10 years of age, motor function was assessed [5]. May et al. [5] reported that there was no association between the number of D4Z4 repeats, sex, race, BMI, and motor performance. However, in this study being underweight was associated with lower quantitative and manual muscle test scores for some muscle groups; in addition, participants with $\leq$4 D4Z4 repeat units had higher clinical severity values, compared to those with >4 repeats (data not shown). The authors found that earlier age at onset of facial weakness correlated with greater disease severity, while age at onset of shoulder weakness was not associated with any motor functional measure. Therefore the authors suggested to capture the age at onset of facial weakness accurately, e.g., by review of family photographs to reduce recall bias [5].

Recently, a prospective cross-sectional study of 28 Dutch patients with early-onset FSHD (defined according to Brouwer et al. [7]) was published [6] and added new insights into the clinical spectrum. Patients with early-onset FSHD had a significantly higher FSHD clinical score, a lower MRC sum score, a higher probability to become wheelchair dependent, shorter D4Z4 repeats and a higher proportion of de novo mutations compared with age- or duration-matched classic-onset FSHD. In addition, systemic features were more frequent in early-onset FSHD and included hearing loss, decreased respiratory function, and spinal deformities. Two patients in the early-onset group developed epilepsy, and one patient FSHD-related vision loss (Coats syndrome),

features that were not observed in the classic-onset group [6].

To summarize, our case report illustrates the evolving phenotype of early onset FSHD1 with particular predominance of facial involvement. The patient had a long history of electrophysiological and histological examinations that remained inconclusive and misleading. Instead, drawing a blood sample nowadays is fully sufficient to clarify the diagnosis. We wanted to aid diagnostic acumen for clinicians who see young children with similar facial weakness so that they can order the appropriate molecular test through the genetic laboratory, and thereby avoid unnecessary and potential harmful clinical investigations.

Acknowledgment

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