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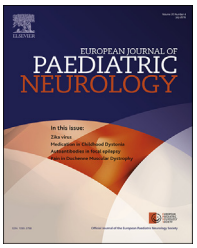

Original article

A 22-year follow-up reveals a variable disease severity in early-onset facioscapulohumeral dystrophy

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ABSTRACT

Aim: To assess the long-term natural course of early-onset facioscapulohumeral dystrophy (FSHD), which is important for patient management and trial-readiness, and is currently lacking.

Methods: We had the unique opportunity to evaluate 10 patients with early-onset FSHD after 22 years follow-up. Patients underwent a semi-structured interview, physical examination and additional genotyping.

Results: Nine initial study participants (median age 37 years) were included, one patient died shortly after first publication. At first examination, one patient was wheelchair dependent, one patient walked aided, and eight patients walked unaided. After 22 years, four patients were wheelchair dependent, three walked aided, and two walked unaided. Systemic features, including hearing loss (56%), intellectual disability (44%), and a decreased respiratory function (56%), were frequent. Patients participated socially and economically with most patients living in a regular house (n = 6) and/or having a paid job (n = 4).

Discussion: Patients with early-onset FSHD generally had a severe phenotype compared to classical onset FSHD. However, after 22 years of follow up they showed a wide variation in severity and, despite these physical limitations, participated socially and economically. These observations are important for patient management and should be taken into account in clinical trials.

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Facioscapulohumeral muscular dystrophy (FSHD, OMIM: 158900) is one of the most prevalent muscular dystrophies.[1] Early-onset FSHD is defined by signs or symptoms of (1) facial weakness before the age of 5 years and (2) shoulder girdle weakness before the age of 10 years, and is considered as a severe subtype of FSHD,[2,3] although information about the natural history is currently lacking. We therefore reassessed a unique cohort of ten severely affected early-onset FSHD patients, which were published as the first genetically confirmed early-onset FSHD-case-series 22 years ago.[4,5]

1. Method

The ten patients with early-onset FSHD described in two case series published by our group in 1994 and 1995[4,5] were all retrieved by the original authors (GWP and OFB) and from the archive of our tertiary referral centre for FSHD. Patients were ranked conform the original table.[5] The study was approved by the local ethics committee and written informed consent was obtained from all patients.

Patients underwent a semi-structured interview on muscle weakness and other symptoms, hearing and vision loss, epilepsy, intellectual disability, spinal or respiratory problems, and daily functioning. Subsequently, a physical examination including manual muscle testing (Medical Research Council scores) and assessment of clinical severity (clinical severity[6] and FSHD clinical scores[7]) was conducted. Wheelchair-dependency was defined as not being able to walk even with walking aids. Visual acuity was measured using a distance acuity chart, with correction if necessary. Respiratory function was tested according to the ATS/ERS criteria,[8] in sitting position using a handheld spirometer (MicroLoop, MicroMedical®) and a face mask. In addition, medical histories were extracted from the initial publications and clinical files.[4,5] The clinical severity score at baseline was estimated based on the available information.

For more accurate genetic analysis, we used high quality genomic DNA isolated from peripheral blood cells. We determined the D4Z4 repeat size and haplotype by pulsed field gel electrophoresis (PFGE); followed by Southern blot hybridization and polymerase chain reaction (PCR) based simple sequence length polymorphisms (SSLP) analysis.[9] Descriptive statistics and linear regression for comparison between D4Z4 repeat length and clinical severity were done using SPSS version 22.

2. Results

Eight patients were examined between October and December 2016, one participated with chart review only, and one died 21 years ago, shortly after first description, due to respiratory infection. The median age at follow-up was 37 years (range 31–58 years, SD 7.9 years). Detailed data on all participants is presented in Table 1. Seven patients had FSHD type 1 with a mean D4Z4 repeat length of 3 units (range 2–5 units). There was a correlation between D4Z4 repeat length and the clinical severity score at follow-up (slope of −1.4, R^2 0.7031, $p = 0.009$). Three complex pathogenic chromosomes were found in this cohort: patient 2 had a contracted D4Z4 repeat at chromosome 10 (previously published as case F4[9]), patient 6 had a p13E-11 deletion, and patient 8 was mosaic for the contraction. All patients had signs from infancy (age 0–1 year). The first sign was facial weakness in all patients, frequently reported as sleeping with the eyes open or an inability to smile. Two patients had an additional symptom simultaneously: scapular weakness (patient 4) and hearing loss (patient 5).

At follow-up, the mean FSHD clinical score was 12/15 (range 6–15, SD 3.1); the mean clinical severity score was 8/10 (range 5–10, SD 2 compared to 6.3/10 at baseline). Four patients (44%) were physically severely impaired and wheelchair dependent. All tested patients had a restrictive pattern respiratory function with four of seven having a forced vital capacity (FVC) below 50% of predicted value based on age, sex, and height. One patient received non-invasive nocturnal ventilation, two patients did not have any signs of nocturnal hypoventilation, and in one patient the finding was new and he was referred for further investigations. Detailed information on the respiratory function and cause of death of the patient who died was lacking. For information on hearing loss, spinal abnormalities, Coat's syndrome, and epilepsy see Table 1.

At a functional level, six patients lived in a regular house, of which four required assistance in self-care. Two patients lived semi-independently in an institution and one patient lived in a full care institution, primarily because of his intellectual disability. The educational level of patients varied from four attending specialized education to three having a bachelor or university level. Four patients had paid jobs matching their educational level and four other patients executed voluntary work. Three patients had a long-term relationship and one patient had children.

3. Discussion

Here we present the natural history of a unique cohort of 10 early-onset FSHD patients with 22-year follow-up with detailed information on physical as well as functional level. The main finding is that early-onset FSHD, known to be at the severe end of the FSHD spectrum, has a variable progressive course. These children grow up to be adults with a variable degree of disease severity and keep their functional abilities and social participation. Most of the patients have severe muscle weakness, and the prevalence of wheelchair dependency is higher compared to the general FSHD population (here: 44% at a mean age of 39 years; in a retrospective cohort: 22% at a mean of 52 years[10]). Early-onset FSHD is therefore rightly considered to be a severe subtype of FSHD with severe muscle weakness and frequent systemic features.[2,3] However, our patients showed remarkable heterogeneity in disease severity at follow-up, which is relevant for patient management and counselling and warrants careful reconsideration of including early onset cases in clinical trials as was suggested based on the assumption of a rapid and more uniform natural history.

Hearing loss, a restrictive pattern of respiratory function, scoliosis, and intellectual disability were frequently reported in this cohort. A new finding is that hearing loss, generally with a

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