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Severe phenotype in infantile facioscapulohumeral muscular dystrophy

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Abstract

While much is known about the clinical course of adult FSHD, the third most common inherited muscular dystrophy, data on the ''infantile phenotype'' and especially on the progression of the disease in children are limited. We have followed a cohort of 7 patients with infantile FSHD for 9–25 years and here report the clinical and genetic findings in this group. Infantile FSHD is relatively rare, amounting to 4% of all of our FSHD patients. Despite some variability in the progression, infantile FSHD has a more consistent phenotype than adult FSHD. Although they had normal motor milestones, all patients showed facial weakness from early childhood, and subsequently were severely affected with rapid progression of the disease, marked muscular wasting, weakness, and hyperlordosis. None of the patients have shown signs of nocturnal hypoventilation or cardiomyopathy so far. No correlation was found between sex and the severity of phenotype whereas all but one patient had very short fragment sizes of the D4Z4 repeat. Only two patients had a de novo mutation: 3 patients inherited the mutation from a parent with somatic mosaicism, and one was inherited from a parent with classical adult FSHD. One patient was unusual in having one allele inherited from his father who showed somatic mosaicism and one allele with an additional de novo mutation. We conclude that infantile FSHD is a severe and rapidly progressive disease, and this needs to be taken into account in the advice given to patients diagnosed in early childhood. However, our data also suggest that the risk to an individual with classical FSHD of having a child with the infantile form is low.

Keywords: Muscular weakness; Infantile onset; Facioscapulohumeral muscular dystrophy

1. Introduction

Facioscapulohumeral muscular dystrophy (FSHD, MIM 158900) is an autosomal dominant disease with an incidence of 1:20 000 – the third most common inherited disease of muscle [1,2]. There is a wide spectrum of severity seen in FSHD, including a so-called infantile form which was first described in 1977 by Brooke [3]. In 1994 Brouwer et al. confirmed that despite the wide range of phenotype FSHD is a genetically homogeneous disorder, and defined criteria for the infantile form of FSHD as (1) signs or symptoms of facial weakness before the age of 5 years and (2) signs or symptoms of shoulder girdle weakness before the age of 10 years [4]. In addition to muscle weakness, infantile FSHD may be associated with sensorineural hearing loss and retinal vasculopathy [5,6]. In classical FSHD the disease is characterized by progressive and highly selective wasting usually beginning with the involvement of facial muscles and the shoulder girdle in the second decade of life [5,7]. The weakness is generally slowly progressive, in what can appear a stepwise fashion. Apart from frequent involvement of the tibialis anterior muscle, it typically moves in a ''descending'' fashion, eventually affecting

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the pelvic girdle which in association with weakness of the abdominal musculature leads to the development of hyperlordosis. Half the patients with adult FSHD show weakness of the pelvic girdle, 10–25% of patients will become wheelchair-dependent, and life expectancy is generally not shortened [2]. Males are typically more severely affected than females, and 30% of patients may not have any problems at all [7–9].

In 1992 Wijmenga and co-workers mapped the FSHD gene to the subtelomere of chromosome 4 (4qter) [10]. In about 95% of cases the disease is associated with the deletion of a variable number of 3.3 kb units of the polymorphic D4Z4 repeat array [11,12]. These units may vary from 11 to 100 copies in unaffected chromosomes whereas in FSHD patients the pathogenic allele is reduced to 1–10 units. In general, a smaller number of units correlates with a more severe phenotype [1,7]. The molecular pathophysiology of FSHD remains unclear with a suspected epigenetic mechanism. About 5% of families with presumed FSHD are not linked to the described locus on 4q35 [13]. Compound heterozygosity has been demonstrated in two families with a possible phenotypic dosage effect [14]. The molecular diagnosis is based on Southern blot and hybridization with probe p13E-11 which recognises a locus proximal to D4Z4. In FSHD patients p13E-11 detects a 10–38 kb fragment after digestion with *Eco*RI. Due to high homology of the 4q35 region to a similar polymorphic repeat array on chromosome 10q26 and therefore cross-hybridization, *Bln*I and *Xap*I can be used to discriminate between 4qter and 10qter derived arrays [15,16]. Two allelic variants of the 4qter subtelomere exist (4qA and 4qB) which are almost equally common in the Caucasian population, but uniquely deletions of the 4qA allele are associated with FSHD [17,18].

To add to the limited data on the progression of the severe infantile form of FSHD, we report on the genetic and clinical aspects of a series of 7 infantile patients under long-term follow-up in Newcastle.

2. Patients and methods

2.1. Clinical assessment

7 patients fulfilling the clinical criteria of infantile FSHD were included into the study. Their case histories were reviewed, and all families and patients were interviewed. Age ranged from 13 to 29 years at the time of the study. They were from 7 families, and have been followed for between 9 and 25 years at the Newcastle Neuromuscular Centre. In all patients, the diagnosis of FSHD had been confirmed on a molecular basis.

Respiratory function was assessed clinically, spirometrically and via overnight pulse oximetry recording. In all patients a formal cardiology assessment including electrocardiogram (ECG) and echocardiogram was performed.

Hearing and vision were assessed by routine audiometry and ophthalmology assessment.

2.2. Genetic analysis

The molecular diagnosis was established applying the method described by Bakker et al. [19]. 4q35 origin of the band <35 kb was identified through reduction by 3 kb after double digestion with *Eco*RI and *Bln*I and probing with p13E-11. The *Eco*RI digest is run in a distinct lane beside the *Eco*RI and *Bln*I digest lane to clearly identify the chromosomal origin of the short band (chromosome 4 versus chromosome 10). With this method fragments smaller than 48 kb can be identified. Somatic mosaicism was identified by comparing signal intensity of the bands within the *Eco*RI and the *Eco*RI + *Bln*I lanes. A similar reduction in intensity of specific bands in both lanes was indicative of mosaicism.

3. Results

3.1. Clinical features: presentation

Age of onset ranged from infancy to 4.5 years. The main clinical features are summarized in Tables 1–3. Gross motor milestones were not delayed in any of the patients. The predominant first presentation was facial weakness: in 5 patients the first recorded symptom was a deficit in eye closure which became most apparent during sleep. The other two patients' first symptom was an inability to smile.

3.2. Distribution of muscle weakness and progression

Only one patient presented with shoulder girdle weakness before the onset of pelvic girdle weakness while four patients had weakness in their pelvic girdle before onset of weakness in the shoulders and upper arms; two patients had onset of weakness in the shoulder and pelvic girdle at the same time. In 5 patients facial weakness lead to difficulties such as dribbling while taking oral food. All patients have various degrees of hyperlordosis which could be extreme (Fig. 1). None developed a kyphoscoliosis. Though none received surgery for their hyperlordosis. Bracing was effective in the short term for some patients in maintaining posture and comfort, one patient has used her brace successfully for 10 years. Foot drop due to tibialis anterior muscle weakness was noted in 4 patients. One patient is still ambulant while the other six are wheelchair-dependent, with a mean age at onset of wheelchair-dependency of 12.3 ± 3.9 years. The mean duration between onset of first symptoms and wheelchair-dependency was 9.9 ± 2.5 years (Table 3).