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Original article

Respiratory management of patients with Fukuyama congenital muscular dystrophy

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Abstract

Background: Fukuyama congenital muscular dystrophy (FCMD), characterized by intellectual impairment associated with cortical migration defects, is an autosomal recessive disorder caused by mutation in the *fukutin* gene. It is the second most common type of muscular dystrophy in Japan. Respiratory dysfunction, along with cardiomyopathy, can be life-threatening in patients with advanced-stage FCMD. However, few reports have focused on this issue.

Methods: We retrospectively studied respiratory dysfunction and therapeutic management in 48 genetically diagnosed FCMD patients (mean age 11.0 years; range 3.6–31.9 years).

Results: Mechanical ventilation was initiated at a median age of 12.1 years in 16 patients, 14 of whom received non-invasive positive pressure ventilation (NPPV) while the other 2 underwent tracheostomy with invasive ventilation (TIV). The two TIV cases had unexpectedly required the initiation of ventilatory support at the ages of 15.7 and 18.0 years, respectively, because of unsuccessful extubation followed by serious respiratory infections, despite rather good respiratory function before these episodes. Patients carrying a compound heterozygous founder mutation or with a severe phenotype tended to need ventilatory support 2–3 years earlier than homozygous patients and those with the typical or mild phenotype. Mechanical insufflation–exsufflation (MI–E) interventions were also employed in six patients with serious dysphagia and were well-tolerated in all cases.

Conclusion: For respiratory management, it is important to regularly evaluate respiratory function in FCMD patients over 10 years of age, since intellectual impairment and insomnia often mask the signs of respiratory dysfunction. Most patients, despite poor cooperation due to intellectual impairment, can tolerate NPPV and MI–E provided that a carefully worked-out plan is adopted.

Keywords: Fukuyama congenital muscular dystrophy; Respiratory management; Mechanical ventilation; Non-invasive positive pressure ventilation; Mechanical insufflation–exsufflation (MI–E)

1. Introduction

Fukuyama congenital muscular dystrophy (FCMD), first reported by Fukuyama et al. in 1960, is the second most common type of muscular dystrophy in Japan [1,2]. It is an autosomal recessive disorder caused by mutation of the *fukutin* gene. FCMD is characterized

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by weakness of facial and limb muscles and brain malformation, resulting in motor impairment, mental retardation, and seizures [1,3]. A 3-kb retrotransposal insertion was detected as the ancestral founder mutation of *fukutin*. With clarification of the pathogenesis of FCMD, the possibility of novel therapeutic approaches was recently raised [4]. Patients carrying a homozygous founder mutation (homozygotes) were reported to manifest better and more homogeneous clinical courses than those carrying a compound heterozygous founder mutation (heterozygotes) [5]. Most FCMD patients are born without serious problems, but develop psychomotor retardation in early infancy. The first feature to be pointed out is usually lack of head control. Later, these patients can typically attain the ability to sit up or slide on the buttocks. Mental retardation is usually severe with intelligence quotient scores between 30 and 50 [1,2]. Respiratory and heart failure are recognized as being among the critical features of advanced-stage FCMD [6,7]. In our recent experience, patients can generally survive approximately to the age of 20 years with respiratory and/or cardiac support. We focused on the cardiac involvement seen in FCMD patients in a prior report [8]. However, to date, there have been only a few studies regarding respiratory involvement [6,7,9]. Respiratory management has improved survival for patients with many types of muscular dystrophy [10–12]. Respiratory problems in other forms of congenital muscular dystrophy have been systematically investigated [13,14]. However, the management strategies routinely applied to other forms of muscular dystrophy may not be fully applicable to FCMD cases because of their severe intellectual impairments. Herein, we describe the characteristics of respiratory management for FCMD patients followed at our hospital.

2. Patients and methods

We retrospectively reviewed the medical records of 48 genetically diagnosed FCMD patients (25 boys and 23 girls) who were followed at Tokyo Women's Medical University. The mean follow-up period was 9.9 years (range: 3.1–31.1 years). Mean age at first observation was 1.5 years (0.1–7.1 years), and at last observation was 11.0 years (3.6–31.9 years). There were 31 patients carrying a homozygous founder mutation and 17 carrying a compound heterozygous mutation (Table 1). Polymorphic microsatellite markers, D9S2105-D9S2170-D9S2171-D9S2107, or the polymerase chain reaction method was used for genetic diagnosis [5]. Maximum motor functions of the patients were classified into the following three groups, as described in our previous publication: patients able to sit unassisted or to slide on the buttocks were considered to have the typical phenotype, those able to stand or walk with or without support the mild phenotype, and those able to sit only with support or lacking head control the severe phenotype [5]. At our institution, FCMD patients are non-periodically examined every 2 or 3 years before 10 years of age, thereafter undergoing routine tests during hospitalization every 1 or 2 years depending on phenotype severity. Overnight end-tidal CO_2 ($ETCO_2$) and saturation O_2 (SpO_2) measurements and blood gas values were determined as parameters of respiratory function. In some cases experiencing anxiety and/or discomfort when using the nasal cannula, in whom it was not possible to perform $ETCO_2$ monitoring, we employed blood catheter placement to obtain blood samples without awakening the patients. Mechanical ventilation was initiated, basically, when hypercapnia ($ETCO_2 >$ 45 mmHg), hypoxemia ($SpO_2 < 95\%$), difficulty with extubation and/or frequent respiratory infections occurred. For ventilation-free probability analysis, we used the Kaplan–Meier method to draw survival curves and the log-rank test and Gehan–Breslow–Wilcoxon test to compare groups. For computation of the odds ratio, we used Fisher's exact test. We set the level of significance at $P < 0.05$ for all analyses.

3. Results

Of the 48 patients with FCMD, mechanical ventilation was initiated for 16 (Table 1). The median age at the start of ventilator use was 12.1 years (range: 1.2–18.0 years). There were seven patients carrying a homozygous mutation (homozygotes) and nine carrying a compound heterozygous founder mutation (heterozygotes). Patients were classified as having the severe, typical or mild phenotype based on their maximum motor ability. The severe, typical, and mild phenotypes were documented in six, nine, and one patient, respectively. Ventilation free probabilities are shown in Fig. 1. In 14 cases, non-invasive positive pressure ventilation (NPPV) had been initiated while the other 2 (patients No.15 and No.16) required tracheostomy with invasive ventilation (TIV). Patients No.6 and No.10 were first administered NPPV just for training purposes, but later developed hypoxemia or hypercapnia as revealed by overnight monitoring. Unexpectedly, TIV became necessary in both patient No.15 and patient No.16, without prior NPPV, due to unsuccessful extubation followed by a severe respiratory infection. Neither of these patients ever satisfied the guideline-recommended extubation criteria [15]. Their respiratory functions before these episodes had been rather good. The differences in various clinical factors, genotypes, seizure history, motor function, and mental status between those with and without mechanical ventilation were also analyzed but no significant differences were identified (Table 2). We were particularly interested in the possible associations of age at the initiation of mechanical ventilation with genotype and maximum motor function. The heterozygotes