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Insomnia in Patients with Fukuyama Congenital Muscular Dystrophy

Takatoshi SATO[1], Keiko ISHIGAKI[1], Sachiko KAJINO[1], Takashi SAITO[1], Terumi MURAKAMI[1], Ikuko KATO[1], Makoto FUNATSUKA[1], Kayoko SAITO[1,2] and Makiko OSAWA[1]

[1]Department of Pediatrics, Tokyo Women's Medical University School of Medicine
[2]Institute of Medical Genetics, Tokyo Women's Medical University

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Fukuyama congenital muscular dystrophy (FCMD) is the second most common type of muscular dystrophy in Japan. It is characterized by congenital muscular dystrophy with central nervous system involvement. Insomnia is often seen in patients with FCMD and can be a serious problem that bothers their families at home. However, there has been no study describing this troublesome symptom in FCMD patients. We retrospectively examined the prevalence, associated factors and pharmacological treatment of insomnia in 47 genetically diagnosed FCMD patients. The prevalence was 15/47 patients (32%), with difficulty falling asleep in 9 patients, difficulty staying asleep in 5, and early waking in one. Eight patients were treated with several kinds of narcoleptics;however, all patients showed resistance to medication. Only 3 patients obtained good control in falling asleep with etizolam or estazolam, and one patient seemed to have a good response to a new narcoleptic, melatonin.

Key Words: Fukuyama congenital muscular dystrophy, insomnia, narcoleptic

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 in *fukutin* (*FKTN*), clinicopathologically characterized by dystrophic changes in skeletal muscle and brain malformation, resulting in motor impairment, mental retardation, and seizures[3)~5)]. Insomnia is also a clinical problem often experienced in patients with FCMD, and may seriously bother patients' families since it is often uncontrollable. Sleep disturbance has been well investigated in other neurodevelopmental disabilities and psychiatric disorders, such as chromosome aberration, attention-deficient / hyperactivity disorder (ADHD), anxiety disorder and major depressive disorder, and the higher prevalence of insomnia in these conditions is already recognized[6)~8)]. However, the features of insomnia in FCMD, even its prevalence, have not been fully clarified. Sleep disturbance, especially insomnia, can affect the quality of life of patients and their families. In this study, we examined the prevalence, onset age, and associated factors including developmental level and seizures in FCMD patients. The effectiveness of narcoleptics was also evaluated.

Patients and Methods

We retrospectively reviewed the medical records of genetically diagnosed FCMD patients who were followed for more than 3 years at Tokyo Women's Medical University (Table 1). From 1989 to 2010, 47 patients (23 boys and 24 girls) were examined.

Table 1 Clinical characteristics of study cohort

	Patient number (age)
Boys/Girls	23/24
FKTN 3 kb insertion Homozygous/Heterozygous	32/15
Age at first observation	1.6±1.5 y (0 y1 m-7 y1 m)
Age at last observation	10.9±4.8 y (3 y7 m-27 y10 m)
Follow-up period	9.5±4.5 y (3 y1 m-26 y1 m)

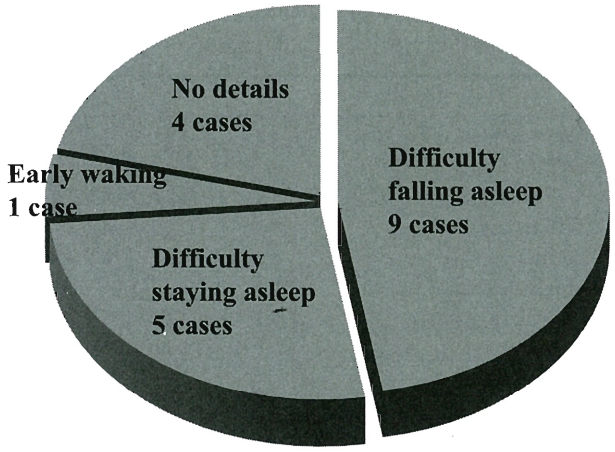

Fig. 1 Types of insomnia
There is overlap of cases included in this graph, because 4 patients had 2 types of insomnia.

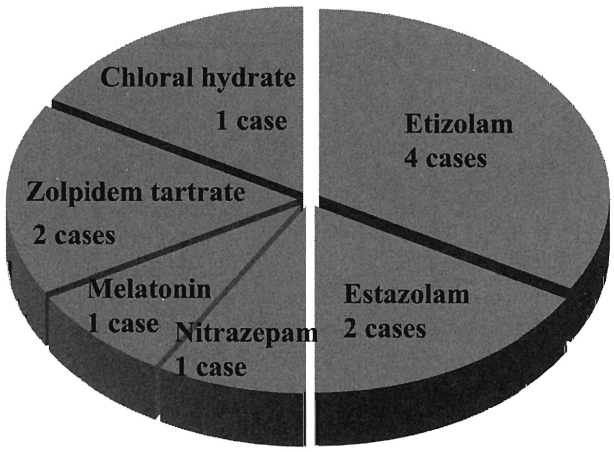

Fig. 2 Administration of narcoleptics
Eight patients were administered narcoleptics. There is overlap of cases included in this graph, because 4 patients were administered 2 or more agents. However, no patient received combination therapy.

Mean follow-up period was 9.3 ± 4.5 years. Mean age at first observation was 1.6 ± 1.5 years and at last observation was 10.9 ± 4.8 years. There were 32 patients carrying a homozygous founder mutation and 15 patients carrying a compound heterozygous mutation. Polymorphic microsatellite markers, D9S 2105-(FCMD)-D9S2170-D9S2171-D9S2107 or polymerase chain reaction were used for genetic diagnosis[9]. Advice on environmental factors such as maintaining an appropriate (cooler) temperature, silence, and darkness of the room, promoting passive stretching body movement after taking a bath in patients who are not able to move by themselves, giving high-carbohyrate drinks when they are not able to sleep, and using a comfortable mattress with automatic air movement was given. Insomnia was diagnosed based on complaints from the patients' families recorded in the medical record, even after families had taken the above advice. In patients who received narcoleptics, the effectiveness was evaluated as "effective", "not effective" or "equivocal" by patients' families. The relationship between insomnia and other factors, genotype, seizures, maximum motor function and mental status, were analyzed statistically. Maximum motor function was classified into three groups, "mild", "typical" and "severe". "Mild" was defined as being able to stand or walk with or without support. "Typical" patients were able to sit without support or to slide on the buttocks. "Severe" was defined as being able to sit only with support or no head control[9]. Chi-squared test, or Fisher's exact probability test when n was less than 5, was used for comparisons between the two groups.

Results

The prevalence of insomnia in this study was 15 of 47 patients (32%). Among them, 6 patients had difficulty falling asleep, 5 difficulty staying asleep, and one early waking. In 4 patients, the medical records were not sufficient for classification of insomnia (Fig. 1). Age at insomnia onset in 13 patients ranged from 5 years 7 months to 16 years 11 months (median: 10 years 10 months). The onset age in the other 2 patients could not be clarified. Eight patients were administered narcoleptics, such as etizolam, estazolam, nitrazepam, melatonin, zolpidem tartrate and chloral hydrate (Fig. 2). No narcoleptic was effective for insomnia in these patients. Three patients tried two types of narcoleptics and one patient required three types, but they did not try combination therapy. Etizolam, estazolam and melatonin were evaluated as "effective" for difficulty falling asleep, although two families did not evaluate the effectiveness of etizolam. Nitrazepam, zolpidem tartrate and chloral hydrate seemed to have no effectiveness, although they were not fully evaluated (Table 2). There was no statistically sig-

Table 2 Effectiveness of narcoleptics

	Effective	Not effective	Equivocal
Etizolam	2	2	0
Estazolam	1	0	1
Nitrazepam	0	0	1
Melatonin	1	0	0
Zolpidem tartrate	0	1	1
Chloral hydrate	0	1	0

There is overlap of the cases included in this table, because 3 patients were administered 2 or more types of medication.

Table 3 Relationship between insomnia and genetic or clinical factors

Insomnia	(+)	(−)	*P*-value
Total number of patients	12	35	
FKTN 3 kb insertion			
Homozygotes	9	23	0.359
Heterozygotes	3	12	
Seizures	12	27	0.054
Maximum motor function			
Typical	10	27	0.270
Severe	2	9	
Mental status			
Meaningful words (+)	7	19	0.508
(−)	4	14	
No details	1	3	

There was no statistically significant difference in insomnia by genotype, seizures, maximum motor function or mental status by Fisher exact test.

nificant difference in the relationship between insomnia and genotype, seizures, maximum motor function and mental retardation. However, all patients with insomnia had seizures (Table 3).

Discussion

This report describes insomnia in patients with FCMD. Thirty-two percent of our FCMD patients had insomnia, which was much lower than our expectation. In some patients, insomnia appeared only while away from home, during hospitalization or traveling;therefore, we could expect a higher prevalence in this cohort. Because this was a retrospective study based on medical records, the prevalence may have been underestimated. The prevalence of insomnia in the general pediatric or adolescent population ranges between 0.05% and 20%[10)~13)]. Since the prevalence of insomnia can be easily affected by the study design, such as diagnostic criteria or study population, the results are very variable among reports[13)]. Therefore, it is hard to simply compare the prevalence between our study and others, but the prevalence reported in our study seems to be higher than that in the general pediatric population. Another limitation of this study is the diagnosis of insomnia itself. We could not apply the international criteria of insomnia in the Diagnostic and Statistical Manual of Mental Disorder (DSM) or International Classification of Diseases (ICD) to FCMD patients, since most of them cannot describe their insomnia in detail.

In this study, insomnia was evaluated based on the families' complaints, because most of the patients with FCMD had mental retardation and could not complain themselves and no objective findings caused by insomnia could be detected. We would like to emphasize that the main problem caused by insomnia was disturbance of the families' quality of life (QOL).

Insomnia is well known to occur in other neurodevelopmental disorders, such as ADHD, and there is extensive experience of the use of medication for treatment. Alpha-agonists, late-day stimulants, antihistamines and antidepressants are often prescribed for sleep disturbance in patients with ADHD[14)]. Contrary to the well-established use of medication in other neurodevelopmental disorders, there are no publications on medication for insomnia in FCMD. In this study, etizolam, estazolam, nitrazepam, melatonin, zolpidem tartrate and chloral hydrate were used in 8 patients. Etizolam, estazolam or melatonin was effective in 3 patients with difficulty falling asleep, but another 2 patients with difficulty falling asleep did not respond to etizolam. Zolpidem tartrate was used for difficulty falling asleep in 2 patients, but its effectiveness was unclear. Chloral hydrate was administered to 1 patient with difficulty staying asleep, but it was not effective. Later, estazolam was effective in the same patient. These results suggest that etizolam may be relatively effective for difficulty falling asleep in FCMD, although the patient number in this study was too small to reach a definite conclusion.

Respiratory failure due to weakness of respiratory muscles is well recognized in patients with

FCMD. In fact, 10 patients in this cohort were diagnosed with chronic respiratory failure (CRF), 9 patients were receiving non-invasive positive pressure ventilation (NIPPV), and 1 patient was under mechanical ventilation with a tracheostomy. Three patients had CRF before the onset of insomnia. Non-controlled respiratory failure is thought to affect sleep;however, we periodically check the respiratory condition by overnight pulse oximetry as the need arises. Furthermore, in these 10 patients with CRF, it was evaluated whether their ventilators were suitable or not, and their respiratory condition was shown to be well controlled under the current respiratory therapy. Therefore, sleep disturbance in this cohort was thought not to be greatly influenced by respiratory condition. Since narcoleptics could also affect respiratory depression, their respiratory function had been evaluated before and after administration, and it was found that no case with respiratory depression was caused by narcoleptics.

Patients who are heterozygotes for the founder mutation are reported to manifest a severe phenotype[9)15)]. We analyzed the relationship between insomnia and other factors;genotype, seizures, maximum motor function and mental status. However, we could not find any statistically significant correlation of these clinical factors, even genotype. Thus, insomnia was independent of these factors, and no insomnia-genotype relationship could be observed.

Itoh et al reported abnormality of catecholaminergic neurons in the brainstem in FCMD, and suggested this may contribute to brainstem dysfunction and may be related to sleep-wake regulation disorder[16)].

Conclusion

In the present study, insomnia was reported in 32% of patients with FCMD. Our results showed that etizolam, estazolam or melatonin may improve insomnia, although the patient group was small. We need to accumulate more patients and conduct further evaluation to confirm these preliminary findings.

Insomnia in FCMD should be considered a CNS complication, and a positive therapeutic approach should be adopted. To improve QOL of patients and their families, medication for insomnia in FCMD should be established.

The authors do not have any conflicting interest.

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福山型先天性筋ジストロフィーにおける不眠の検討

[1]東京女子医科大学医学部小児科学
[2]東京女子医科大学附属遺伝子医療センター
佐藤 孝俊[1]・石垣 景子[1]・梶野 幸子[1]
齊藤 崇[1]・村上てるみ[1]・加藤 郁子[1]
舟塚 真[1]・斎藤加代子[1,2]・大澤眞木子[1]

福山型先天性筋ジストロフィー(Fukuyama congenital muscular dystrophy：FCMD)は，顔面筋罹患および中枢神経系の合併を特徴とし，本邦において，Duchenne 型筋ジストロフィーに次いで，二番目に多い筋ジストロフィーである．不眠は，FCMD 患者にしばしば合併し，在宅療養での問題の一つとなる．特に，外泊先での不眠が問題となることが多く，家族は，その管理に難渋するため，患者および家族の quality of life は大きく損なわれる．しかし，我々の検索し得た範囲内で，FCMD の不眠に関する研究は今までに報告がなく，広汎性発達障害をはじめとする，他の神経疾患・発達障害のように，知見の蓄積や確立された治療方針もない．今回，我々は，当科で 3 年間以上継続して経過観察し，遺伝子検査にて確定診断した FCMD 患者 47 名の不眠について，後方視的に検討した．不眠の合併頻度は，47 名中 15 名（32%）であり，入眠困難を 9 名，中途覚醒を 5 名，早朝覚醒を 1 名に認めた．8 名に対して，各種睡眠薬が使用されていたが，どの薬剤も，家族が満足を得られるまでの明らかな有効性は確認できなかった．しかし，入眠困難を呈した 3 名に対し，エチゾラムおよびエスタゾラムは，睡眠導入に関して一定の有効性は示された．さらに，最近本邦でも，その使用が拡大されてきているメラトニンも，同じく入眠困難を示した患者 1 名に試用され，その有効性が示唆された．今回の検討では，FCMD 患者に不眠の合併が多いことが示されたが，有効な睡眠薬に関しては使用例が少なく，有効な候補薬を示すに留まり，十分な検討には至らなかった．