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Case Report

Clinical remission of myopathy with MYH2 deficiency after precision medicine-developed rehabilitation: a case report

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Abstract: Here, we describe the case of a motor developmental disorder associated with intellectual disability accompanied by *MYH2* mutations (c.2266G>A and c.4258C>T) in a female child in China. Her initial detailed functional rehabilitation evaluation gauged motor skills, balance, verbal language, and daily living skills. A general therapy plan was then established to enhance balance, muscle strength in the lower extremities, walking, gross and fine motor function, and family education. Clinicians and therapists later modified her rehabilitation regimen after her *MYH2* mutations were identified by adding specific mobility and endurance exercise to the original plan. The clinical remission of myopathy with *MYH2* missense mutations was observed in the patient after this targeted rehabilitation, indicating that precision therapy is very effective for developing a suitable rehabilitation program for patients with unexplained myopathies.

Keywords: *MYH2*, myopathy, rehabilitation treatment, precision medicine

Introduction

The diagnosis and treatment of myopathy has been challenging for clinicians, although recent molecular biological techniques has enabled early and clear diagnosis of myopathy caused by inherited genetic or metabolic factors [1, 2]. However, the effective treatment of this condition remains difficult. Gene therapy and stem cell transplantation have produced breakthroughs in myopathy research, but risks associated with the adeno-associated virus vector and stem cell tumorigenicity have limited the successful applications of these therapeutic approaches in clinical contexts [3, 4]. Presently, rehabilitation therapy is the major option for patients diagnosed with myopathy [5].

Precision medicine is a newly emerging method for treating myopathy that accounts for individual differences in genes and the environment of each patient. Patients with similar symptoms but different disease etiologies benefit from precision rehabilitation medicine. For example, although muscle intolerance to fatigue is a clinical manifestation of both mitochondrial and muscular dystrophy, the treatment program for each differs because of their distinct genetic causes.

Rare variants in certain genes are associated with myopathy, such as the myosin heavy chain 2 (*MYH2*) gene, which is responsible for myopathy and ophthalmoplegia (OMIM #160740). The gene is expressed in fast-twitch 2A muscle fibers and encodes a myosin heavy chain isoform. *MYH2* mutations can cause varying levels of muscle weakness in different parts of the body and lead to abnormal numbers or size of 2A muscle fibers [6]. *MYH2* mutations can

Table 1. Detailed evaluations of the patient's initial, 1st phase, and 2nd phase functional status

Rehabilitation Evaluation Content		First Rehabilitation Evaluation		After 1st Phase of Rehabilitation		After 2rd Phase of Rehabilitation (Optimized)	
Peabody Developmental Motor Scales-2 (PDMS-2)		RS	AE	RS	AE	RS	AE
Gross Motor Quotient (GMQ)	Stationary	36	11	37	14	39	21
	Locomotion	60	10	68	12	93	19
	Object Manipulation	4	12	9	15	19	23
Fine Motor Quotient (FMQ)	Grasping	42	20	43	28	46	40
	Visual-motor Integration	86	20	90	22	101	28
Gross Motor Function Measure (GMFM-66)		Percentage		Percentage		Percentage	
	Lying and Rolling	100		100		100	
	Sitting	100		100		100	
	Crawling and Kneeling	69.25		Not test		Not test	
	Standing	61.54		Not test		Not test	
	Walking, Running, and Jumping	52.78		Not test		Not test	
The Functional Independence Measure for Children (WeeFIM)							
	Self-care Ability	13		15		22	
	Motor Ability	8		11		25	
	Cognitive Ability	11		13		18	
	Total	32		39		65	
Huang Zhoming-Han Zhijuan Test (HHT)		0		5.4		16.2	
Vocabulary Comprehension Test for Children-Revised (VCTC-R)		15		25		50	

RS: Raw Score, AE: Age Equivalent.

exhibit either dominant and recessive inheritance and cannot be accurately predicted based solely on a patient's family medical history [7]. Morphological and molecular genetic analysis are required to accurately diagnose this disease. To date, only a few studies have focused on the treatment strategy for abnormal symptoms in patients with *MYH2* mutations, and no guidelines are available to clinicians for specifically addressing different mutations. In the current study, we report the successful use of precision rehabilitation medicine in a patient with two *MYH2* missense mutations. Individualized comprehensive rehabilitation training approaches can significantly help patients in various ways, including alleviating symptoms, increasing independent living capacity, and improving quality of life.

Case report

Case description

A 35-month-old Chinese female who presented with gross and fine motor developmental disorders associated with intellectual disability was admitted to our rehabilitation department at Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. Further investigation of her medical history revealed that the patient's mother had developed diabetes during the pregnancy and that the patient exhibited intrauterine growth retardation at 30 weeks gestation. The patient showed no evidence of disease prior to the above clinical observations. After presentation, she was initially diagnosed with developmental retardation with suspicion of cerebral palsy and was advised to undergo further rehabilitation evaluation. In addition, there was no family history of neurodevelopmental disorders and motor developmental disorders.

Rehabilitation evaluation

On admission, a physical examination of this patient revealed decreased muscle strength (grade IV) and muscle tone for the lower limbs and facial muscles, grade III sitting balance, grade II standing balance, poor one-legged standing balance, and unstable walking. The Gesell intelligence developmental test showed intellectual disability. In addition, a detailed functional rehabilitation evaluation of the patient revealed that her gross and fine motor skills, balance, verbal language, and daily living

Table 2. Modified rehabilitation strategy based on genetic etiology of the patient's myopathy

Type of Training	Approaches
Endurance Exercise (Optimized)	Exercise on a stationary bicycle for 15 minutes at moderate intensity, twice per day, 3 days/week. The training time can be gradually increased to 30 minutes per session.
Eye Movement Exercise (Optimized)	Move eyes in different directions to track a moving ball in the therapist's hand.
Ambulation Exercise (Optimized)	Sit-to-stand training; stand-to-sit training; squat-to-stand training; walking activities, such as walking forward and backward and turning around an obstacle; and stair activity training, such as climbing stairs with various step heights.
Balance Exercise (Original)	Weight shifting; single-leg supporting training; and balance plate training, such as playing ball with a therapist with both legs standing on a balance plate or during single-leg standing.
Motor Skill Training (Original)	Jumping forward and upward; kicking large and light balls; and throwing a ball at different targets.
Strength Training (Original)	Strengthening the masseter muscle, the hip, knee and ankle extensors and flexors, and muscles of the shoulder girdle via resistance training against the patient's own gravity and neuromuscular electrical stimulation once daily.

Original: Activities included in the first therapy plan developed after the patient's initial evaluation. Optimized: Activities added to the first therapy plan after the patient's genetic diagnosis.

skills were delayed through Peabody Developmental Motor Scales-2 (PDMS-2) [8], Gross Motor Function Measure (GMFM-66) [9], The Functional Independence Measure for Children (WeeFIM) [10], Huang Zhoming-Han Zhijuan Test (HHT) [11] and Vocabulary Comprehension Test for Children-Revised (VCTC-R) [12] (**Table 1**).

Initial rehabilitation interventions

Based on the patient's comprehensive assessment described above, a general rehabilitation plan was established that involved training in balance, muscle strength in the lower extremities, walking, gross and fine motor function, and family education (**Table 2**). This intervention program consisted of 45-min sessions 3 days per week for 4 weeks (total of 12 sessions). After this first phase of training, her gross and fine motor skills and balance had only mildly improved (**Table 1**).

Precision rehabilitation interventions

During the initial therapy phase, genetic testing was performed to determine an accurate diagnosis and improve the patient's rehabilitation strategy. As described above, this patient had no known relevant disease history but did not respond well to general rehabilitation. This presentation strongly suggested that genetic defects related to myopathy or motor developmental retardation should be considered. Whole-exome sequencing was performed, and novel heterozygous mutations (c.2266G>A and c.4258C>T; p.Leu1420Phe and p.Asp756Asn) were identified in the *MYH2* gene (**Figure 1**) predicting to be pathogenic and to potentially lead to proximal myopathy and extraocular muscle paralysis mainly due to impairment of type 2A muscle fibers [13]. The physician suggested muscle biopsy for the patient, but her parents declined the procedure. Thus, clinicians and therapists modified her treatment strategy based on existing research on *MYH2* mutations, which reported that endurance training in patients with myosin myopathy may be an important way to improve their motor function. Functional mobility and endurance exercises were added to the initial rehabilitation training program to shift expression of the myosin heavy chain isoform from fast to slow (**Table 2**). The modified training program (the second phase of rehabilitation) consisted of 45-min sessions 3 days a week for 12 weeks.

Results

After optimized precision rehabilitation, the patient's gross and fine motor function notably improved as indicated by stationary, locomotion, object manipulation, grasping, and visual-motor integration tests. In addition, her ability to stand, walk, and jump was markedly enhanced compared to her progress after the initial therapy phase (**Table 1**), which did not consider the genetic etiology of her myopathy.

Discussion

Here, we report a case involving the successful physical rehabilitation of a child with motor developmental delay caused by *MYH2* gene mutations. Clinical rehabilitation strategies were optimized after a precision diagnosis and etiology had been determined. After a modified 12-week rehabilitation program, the patient's

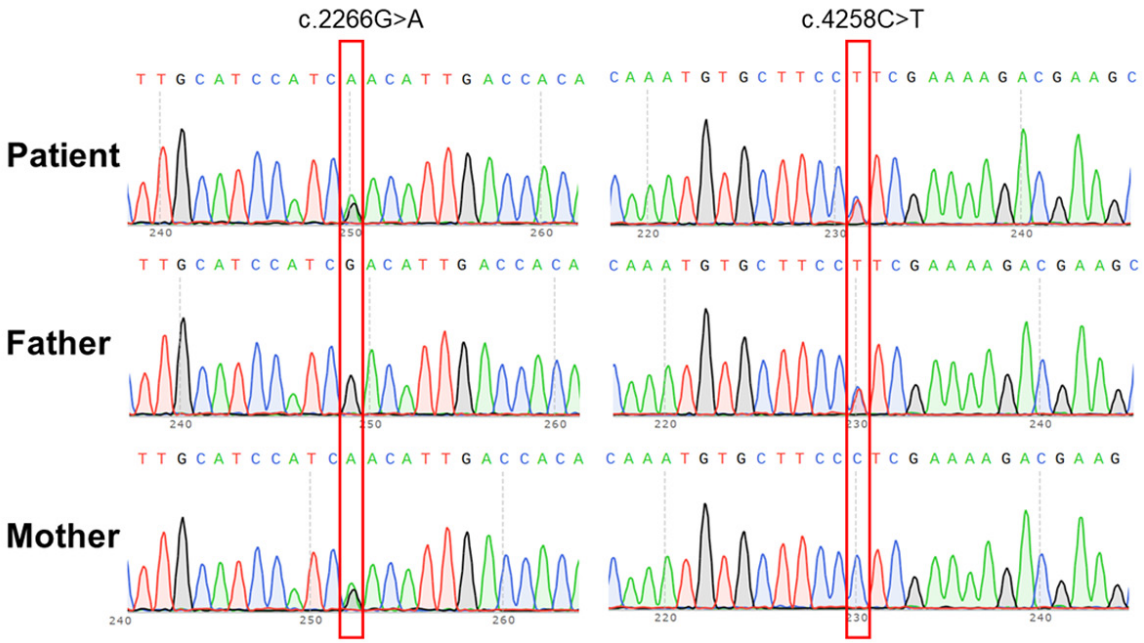

Figure 1. Electropherograms of the patient and her immediate family. Whole-exome sequencing revealed two heterozygous missense mutations in the patient's *MHY2* gene resulting in Leu1420Phe and Asp756Asn substitutions. Red boxes indicate mutation sites.

Table 3. Comparative clinical presentation of *MYH2* mutations

Clinical characteristics of *MYH2* mutation(s)	This case
Appearance	
Myopathic facies [14, 18, 19]	Mild
Ptosis [18]	N
High-arched palate [19]	N
Scapular winging [19]	N
Musculoskeletal	
External ophthalmoplegia [13, 14, 18-20]	Mild
Proximal muscle weakness [13, 19, 20]	Mild
Neck muscle weakness [13, 19]	Mild
Effects on upper and lower limbs [13]	Mild-moderate
Distal muscle weakness [13, 19]	Mild
Generalized muscle weakness [14]	Mild
Inclusion body myositis [15, 21]	Y
Congenital joint contracture [20]	N
Scoliosis [18, 19]	N
Neurologic	
Waddling gait [18]	Mild
Muscle biopsy findings	
Predominance of type 1 fibers [13, 18, 19]	NI
Loss of type 2A fibers [13, 18, 19]	NI
Fiber size variability [13, 14]	NI
Others	
Eye movement disorders [19, 22, 23]	N

Y, yes; N, no; NI, not investigated.

balance and motor function markedly improved compared to the initial therapy plan that did not account for her MYH2 deficiency.

The *MYH2* gene encodes the myosin heavy chain isoform expressed in fast-type 2A muscle fibers, which are mainly used during sustained power activities. *MYH2* mutations can lead to autosomal dominant or recessive diseases [7], although most patients with recessive *MYH2* mutations can gain independent living ability after appropriate treatment [13, 14]. In 2000, Martinsson et al. first reported a family with joint contractures, proximal muscular weakness, and extraocular muscle paralysis caused by a missense mutation in *MYH2* (c.2116G>A; p.Glu706Lys) [15]. Subsequently, several studies reported various novel mutations in the *MYH2* gene (**Table 3**), which can produce many similar symptoms, such as disease-specific myopathy and extraocular paralysis. However, different mutations can also lead to distinct clinical features, including joint contracture, muscular dystrophy, myalgia, oculomotor disorders, and abnormal gait. Interestingly, the onset time for clinical signs and symp-

toms caused by *MYH2* mutations does not consistently correlate with severity. In the patient's case reported here, the presence of novel heterozygous missense *MYH2* mutations was determined after her clinical presentation and lack of relevant medical history raised concerns. She showed generalized muscular weakness and delayed motor development at infancy, and her signs and symptoms worsened with age. Although the patient's parents did not consent to a muscle biopsy, several previous studies have indicated that various pathological muscle changes occur in patients with *MYH2* mutations, especially small or absent type 2A muscle fibers [13, 14, 16]. From this present case report, reduced expression of *MYH2* or presence of abnormal type 2A muscle fibers can be overcome by tailored exercise that target potential disease-specific symptoms and signs in order to promote the growth and development of normal muscle fibers, resulting in improved motor function. Therefore, clinicians and therapists promptly adjusted the patient's rehabilitation regimen after her genetic diagnosis had been determined.

Certain conditions, such as endurance training, can induce a shift from fast to slow myosin heavy chain isoform expression [17]. Although various types of endurance training may be effective, given the patient's young age and low muscle strength, a lower limb power bicycle was adopted as a training device. Time, workload, and distance can be quantified using the power bicycle, so progress was easy to observe. Similarly, in cases involving adult patients with *MYH2* mutations, cycling endurance training significantly improved work efficiency and walking speed [16]. Furthermore, childhood is an important period for neuromuscular system development, although children with *MYH2* mutations cannot complete certain daily functional activities due to muscle weakness, resulting in their reduced willingness to perform them. Thus, many training exercises to promote spontaneous movements were added to our patient's rehabilitation program. Through interactive games in the present study, we tried to encourage her to complete age-appropriate daily life activities, thereby reducing her dependence on her parents. In addition, given the characteristics of muscle physiology in children, we did not aim to increase muscle volume but instead sought to improve her neuromuscular coordination via various forms with respect to muscle coordination via various forms of anti-gravity training, such as overhead claps, standing vertical jumps, and sit-ups. For functional weakness in muscles of the inner thighs, hip girdle, and shoulder girdle, we used functional electrical stimulation to avoid muscle atrophy.

Patients with myopathy may present with motor retardation that can be severe and disabling, but the disease has no uniform treatment. Therefore, early and accurate genetic diagnosis that indicates potential disease-specific symptoms and signs, and consequently informs an effective rehabilitation is critical for a positive outcome. In our case, the patient's neurodevelopmental problems were initially more concerning than her other clinical signs, so we first focused on promoting normal development of her neurological system. However, per detection of her *MYH2* mutations, we developed an optimized treatment strategy based on an extensive literature review of *MYH2* gene that led to marked improvement in the patient's overall motor function.

Conclusion

This report provides the first description of the clinical remission of myopathy associated with *MYH2* missense mutations after rehabilitation optimized based on genetic diagnosis. We conclude that precision therapy is critical for treating patients with unexplained myopathies with a targeted and effective therapy program. This is a single case report. Conclusion here is only indicative, but not generalizable.

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Disclosure of conflict of interest

None.

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