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ORIGINAL ARTICLE

Mucopolysaccharidosis III in Taiwan: Natural history, clinical and molecular characteristics of 28 patients diagnosed during a 21-year period

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Mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome) has a variable age of onset and variable rate of progression. However, information regarding the natural history of this disorder in Asian populations is limited. A retrospective analysis was carried out for 28 patients with MPS III (types IIIA [n = 3], IIIB [n = 23], and IIIC [n = 2]; 15 males and 13 females; median age, 8.2 years; age range, 2.7–26.5 years) seen in six medical centers in Taiwan from January 1996 through October 2017. The median age at confirmed diagnosis was 4.6 years. The most common initial symptom was speech delay (75%), followed by hirsutism (64%) and hyperactivity (54%). Both z scores for height and weight were negatively correlated with age (r = −.693 and −0.718, respectively; p < .01). The most prevalent clinical manifestations were speech delay (100%) and intellectual disability (100%), followed by hirsutism (93%), hyperactivity (79%), coarse facial features (68%), sleep disorders (61%), and hepatosplenomegaly (61%). Ten patients (36%) had epilepsy, and the median age at the first seizure was 11 years. Thirteen patients (46%) experienced at least one surgical procedure. At the time of the present study, 7 of the 28 patients had passed away at the median age of 13.0 years. Molecular studies showed an

Abbreviations: AC, air conduction; BMD, bone mineral density; CT, computed tomography; DXA, dual energy X-ray absorptiometry; ECG, electrocardiography; EEG, electroencephalography; GAGs, glycosaminoglycans; HAZ, height-for-age z score; MPS, mucopolysaccharidosis; MRI, brain magnetic resonance imaging; OAHI, obstructive apnea–hypopnea index; SD, standard deviation; WHO, World Health Organization.

allelic heterogeneity without clear genotype and phenotype correlations. MPS IIIB is the most frequent subtype among MPS III in the Taiwanese population. An understanding of the natural history of MPS III may allow early diagnosis and timely management of the disease facilitating better treatment outcomes.

KEYWORDS

clinical manifestations, diagnosis, management, mucopolysaccharidosis III, natural history

1 | INTRODUCTION

Mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome) is a group of four autosomal recessive lysosomal storage disorders resulting from a deficiency in one of the four enzymes involved in the degradation of heparan sulfate. The four subtypes of MPS III (types A–D) are caused by the deficiency of: heparan *N*-sulfatase in type A (OMIM 252900), alpha-*N*-acetylglucosaminidase in type B (OMIM 252920), acetyl CoA-alpha-glucosaminide acetyltransferase in type C (OMIM 252930), and *N*-acetylglucosamine 6-sulfatase in type D (OMIM 252940) (Neufield & Muenzer, 2001; Chuang & Lin, 2007). MPS III has a variable age of onset and diverse rate of progression. The primary characteristic of MPS III is the degeneration of the central nervous system, leading to intellectual disability and hyperactivity. Common presenting somatic features include coarse facial features with broad eyebrows, hirsutism, skeletal dysplasia, degenerative joint disease, hepatosplenomegaly, macrocephaly, and hearing loss (Fedele, 2015).

There are three stages for the clinical evolution of MPS III. The first stage is during the first 1–2 years of life. After an initial normal development, developmental delay becomes apparent. The second stage begins around 3 and 4 years. Progressive mental deterioration and severe behavioral problems emerge and ultimately lead to severe dementia. In the final stage, behavioral problems slowly disappear, but motor retardation with swallowing difficulties and spasticity appear. Patients usually pass away before the beginning of the third decade of life, although longer survival has been observed in patients with an attenuated phenotype (Valstar, Ruijter, van Diggelen, Poorthuis, & Wijburg, 2008).

The incidence of MPS III differs among different populations. Reported rates range from 1 in 53,000 live births in the Netherlands to 1 in 340,000 live births in British Columbia (Applegarth, Toone, & Lowry, 2000; Poorthuis et al., 1999). In Taiwan, the incidence of MPS III is approximately 1 in 255,000 live births, with most of these patients having MPS IIIB (Lin et al., 2009). The individual incidences of MPS III subtypes also revealed large variations between different countries. In northern Europe (including France, Germany, the Netherlands, Sweden, and the UK), MPS IIIA is the most prevalent subtype; however, in southern countries (including Greece and Portugal), MPS IIIB predominates (Héron et al., 2011). The founder effect may account for the discrepancy of the incidence in different ethnic populations.

There is currently no effective treatment for MPS III, and patient care is limited to symptom management and palliative support. Disease-specific treatments for MPS III, including intrathecally delivered enzyme replacement therapy, substrate reduction therapy, hematopoietic stem cell transplantation, and gene therapy, are being studied (Fedele, 2015; Jones et al., 2016; Tardieu et al., 2017; Valstar et al., 2008).

There are several reports describing the natural course of MPS III in Caucasian populations (Buhrman, Thakkar, Poe, & Escolar, 2014; Delgadillo, O'Callaghan, Gort, Coll, & Pineda, 2013; Héron et al., 2011; Jansen et al., 2007; Malm & Månsson, 2010; Meyer et al., 2007; Ruijter et al., 2008; Truxal et al., 2016; Valstar et al., 2010; Velasco, Sanchez, Martin, & Umaña, 2017). However, information regarding the natural history of this disorder in Asian patients is limited. The purpose of this study was to retrospectively collect and analyze the clinical, molecular and laboratory information recorded on the medical charts of Taiwanese MPS III patients, including medical histories, clinical manifestations and assessments, diagnosis, and symptom management. The data are essential for the early diagnosis of this disorder as well as the development of future therapies (Ghosh et al., 2017).

2 | PATIENTS AND METHODS

A retrospective study was carried out for patients diagnosed with MPS III seen from January 1996 to October 2017 in six medical centers in Taiwan, including Mackay Memorial Hospital, Kaohsiung Veterans General Hospital, China Medical University Hospital, National Taiwan University Hospital, National Cheng Kung University Hospital, and Changhua Christian Children's Hospital. The diagnosis of MPS III was confirmed by measurements of enzymatic activities of particular lysosomal hydrolases in leukocytes or skin fibroblasts, two-dimensional electrophoresis of urinary glycosaminoglycans (GAGs), and/or mutational analysis (Chuang, Lin, & Chung, 2001; Lee-Chen et al., 2002). Information on 28 MPS III patients (types IIIA [n = 3], IIIB [n = 24], and IIIC [n = 1]; 15 males and 13 females; mean age ± SD, 10.1 ± 5.7 years; median age, 8.2 years; age range, 2.7–26.5 years) was collected. Patients' charts were reviewed for medical history, clinical manifestations and assessments, as well as molecular and laboratory studies. Findings on physical examinations were obtained from physicians' records at the outpatient clinic or during admission. Each patient's demographic information, including gender, age at confirmed diagnosis, age at the first seizure, age at and cause of death (if patient

died), molecular and laboratory results, height, weight, ambulatory status at the time of the latest medical records, physical examinations, and surgical interventions (if any) were collected as applicable. Any available results of the following investigations were also recorded: electroencephalography (EEG); brain magnetic resonance imaging (MRI) and computed tomography (CT); laryngoscopy; bronchoscopy; electrocardiography (ECG); echocardiography; hearing assessment by pure-tone audiometry; tympanometry; abdominal ultrasonography; bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA); polysomnography; as well as other information relevant to the course of disease. Kaplan–Meier survival analyses were carried out to manifest probability of survival. Standard deviation (SD) scores (*z* scores) for height and weight were computed using standard growth tables for the Taiwanese population (CChen & Chang, 2010). A *z* score was obtained by subtracting the population mean from each individual's raw score and then dividing the difference by the SD (SD) of the population. Results are expressed as the mean ± SD. ECG and echocardiographic examinations were performed and measurements were compared with normal data as previously described (Henry, Gardin, & Ware, 1980; Lin et al., 2014). For hearing assessment by pure-tone audiometry, the degree of hearing loss was classified by the age-independent World Health Organization (WHO) clinical guidelines (World Health Organization, 1999). In combination with pure-tone audiometry, tympanometry is used to assess the condition of the middle ear and the mobility of the eardrum and conduction bones by creating variations of air pressure in the ear canal. A normal tympanogram is labeled type A. Types B and C tympanograms may reveal a middle ear effusion, perforation or scarring of the tympanic membrane, lack of contact between the conduction bones of the middle ear, or a tumor of the middle ear (Lin et al., 2014). Abdominal ultrasonographic examinations were conducted using high-resolution B-mode ultrasonography (SA-700A, Toshiba, Tokyo, Japan) with a 3.5-MHz curved array transducer. Liver and spleen size were assessed in comparison with the normal reference values for different body heights of children (Konuş et al., 1998). DXA was carried out to evaluate BMD of the lumbar spine (L1–L4), using the Hologic QDR 4500 system (Bedford, MA, USA) (Lin et al., 2013). Polysomnography was performed on the basis of the guidelines of the American Thoracic Society. The obstructive apnea–hypopnea index (OAHI) was calculated according to the number of obstructive/mixed apneas and hypopneas that happened per hour of total sleep time (American Thoracic Society, 1995; Lin et al., 2010). Written informed consent was acquired from a parent for children and from patients over 18 years of age. The study was approved by the ethics committee of Mackay Memorial Hospital, Taipei, Taiwan.

2.1 | Statistical analysis

We calculated descriptive statistics, including means and SDs. The relationship between age and height and weight of the 28 patients with MPS III was determined using Pearson's correlation coefficient (*r*), and significance was tested using Fisher's *r*–*z* transformations. All statistical analyses were carried out using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Statistically significant differences were considered with $p < .05$.

3 | RESULTS

Table 1 revealed the medical histories, laboratory data, and clinical manifestations of 28 patients with MPS III in Taiwan. The percentages of each subtype of MPS III in this study were MPS IIIA (11%), MPS IIIB (86%), and MPS IIIC (3%). No patient with MPS IIID was identified in Taiwan at the time of this study. The most common initial symptom was speech delay (75%), followed by hirsutism (64%) and hyperactivity (54%). The median age at confirmed diagnosis for all 28 patients was 4.6 years. The median ages at confirmed diagnosis for each MPS subtype were 5.2, 4.4, and 8.6 years for MPS IIIA ($n = 3$), MPS IIIB ($n = 24$), and MPS IIIC ($n = 1$), respectively. The mean urinary GAG concentration was 422.3 μg/mg creatinine (reference values are age dependent: 1–3 years, 20.0–110.5; 3–5 years, 10.7–112.0; >5 years, 10.8–77.5 μg/mg creatinine). The mean leukocyte-specific enzyme activity was 0.03 nmol/17 hr/mg protein for MPS IIIA ($n = 3$, heparan *N*-sulfatase, reference range: 4.1–12 nmol/17 hr/mg protein), 0.08 nmol/hr/mg protein for MPS IIIB ($n = 24$, alpha-*N*-acetylglucosaminidase, reference range: 1.4–5.4 nmol/hr/mg protein), and 0.01 nmol/17 hr/mg protein for MPS IIIC ($n = 1$, acetyl CoA-alpha-glucosaminide acetyltransferase, reference range: 8.6–32 nmol/17 hr/mg protein). At the time of enrollment in this study, 18 (64%) of these patients could walk, while 7 (25%) and 3 (11%) were wheelchair bound or bedridden, respectively. At the time of the present study, seven patients had passed away at the mean ± SD age of 13.0 ± 3.0 years (range 7.9–16.7 years, median 13 years): these patients died of pneumonia ($n = 2$, 7.9 and 16.7 years), epilepsy ($n = 1$, 13 years), and unknown cause ($n = 4$). The survival probabilities at 5, 10, 15, 20, and 25 years were 100%, 95%, 58%, 49%, and 49%, respectively (Figure 1). Eight patients (29%) had short stature and two (7%) were underweight with a *z* score of < -2. The mean *z* scores for height and weight at the time of the latest medical records were −0.47 ± 1.97 and 0.02 ± 1.49, respectively. Both *z* scores for height and weight were negatively correlated with age ($r = -.693$ and −0.718, respectively; $p < .01$) (Figure 2). The most prevalent clinical manifestations were speech delay (100%), intellectual disability (100%), hirsutism (93%), hyperactivity (79%), coarse facial features (68%), sleep disorders (61%), and hepatosplenomegaly (61%) (Figure 3). Ten patients (36%) had epilepsy, and the median age at the first seizure was 11 years. The range of age for the first seizure was 1.5–20 years. Thirteen patients (46%) experienced at least one surgical procedure. The most prevalent surgical interventions were craniotomy (11%), percutaneous endoscopic gastrostomy (11%), herniorrhaphy (11%), supraglottoplasty (11%), tonsillectomy (11%), adenoidectomy (11%), followed by ear tube insertion (7%), spinal fusion surgery (4%), and epiphyseal surgery (4%) (Figure 4).

3.1 | Mutational analysis

Sixteen patients had genetic analysis (Table 2). Twenty-one mutations were found, including 14 missense (67%), 2 splicing (10%), 2 frameshift (10%), 2 rearrangement (10%), and 1 nonsense (5%). Fourteen mutations were previously reported in the literature, as well as seven *NAGLU* gene mutations (MPS IIIB) were identified in this report for the first time (Beesley, Jackson, Young, Vellodi, & Winchester, 2005;

TABLE 1 Medical histories, laboratory data and clinical manifestations of 28 patients with MPS III in Taiwan

Patient No.	MPS type	Gender	Age (yr)	Age at diagnosis (yr)	Initial symptoms	Leukocyte specific enzyme activity[a]	Urinary GAG (μg/mg creatinine)[b]	Height (z score)	Weight (z score)	Ambulatory status	Age at the first seizure (yr)	Age at death (yr)	Cause of death
1	IIIB	M	2.7	1.3	Speech delay, hirsutism	0.05	325.6	−1.29	1.37	Walking			
2	IIIB	M	4.2	1.8	Speech delay, hirsutism	0.06	737.8	0.53	1.32	Walking			
3	IIIB	F	4.2	4.2	Hyperactivity	0.01	NA	0.48	2.01	Wheelchair bound		12.1	Unknown
4	IIIB	F	4.2	1.2	Speech delay, unstable gait	0	1087.3	0.94	1.06	Walking	1.5		
5	IIIB	M	4.3	3.3	Speech delay, hyperactivity	0.1	379.3	2.63	3.49	Walking			
6	IIIB	M	5.1	4.7	Hyperactivity, unstable gait	0.4	254.71	3.20	2.91	Walking			
7	IIIB	M	5.3	3.4	Speech delay, unstable gait, and hirsutism	0.07	183.7	2.56	0.52	Walking			
8	IIIB	F	6.3	3.3	Speech delay, unstable gait	0	1142.5	1.42	0.62	Walking			
9	IIIB	F	6.3	4.9	Speech delay, hyperactivity	0.31	262.4	2.02	1.60	Walking			
10	IIIB	M	7.1	4.0	Speech delay, hyperactivity, and hirsutism	0.01	NA	0.31	0.51	Walking		7.9	Pneumonia
11	IIIB	F	7.1	7.2	Speech delay, hyperactivity, and hirsutism	0	NA	−0.08	−0.76	Walking			
12	IIIB	M	7.2	5.9	Hyperactivity	0.1	495.2	0.85	0.51	Walking			
13	IIIB	M	7.5	5.9	speech delay, hirsutism	0.04	241.5	−0.23	−0.56	Walking			
14	IIIB	M	7.8	4.5	Autistic behavior, speech delay	0.01	458.1	0.44	−0.21	Walking			
15	IIIA	F	8.7	3.6	Hirsutism, unstable gait	0.02	364.2	0.95	0.12	Walking	8.5		
16	IIIA	M	9.9	5.2	Speech delay, hirsutism	0	NA	−2.68	−1.13	Bedridden	7	11.3	Unknown
17	IIIB	M	10.9	5.1	Speech delay	0.01	NA	−3.09	−1.16	Bedridden	9.5	15.9	Unknown
18	IIIB	F	11.0	3.6	Speech delay, hyperactivity, and hirsutism	0.01	NA	0.69	0.29	Walking	11		
19	IIIA	F	11.0	11.1	Speech delay, hirsutism	0.08	NA	−2.52	−1.63	Walking	12.5	13.0	Epilepsy
20	IIIB	F	11.4	5.2	Hirsutism, speech delay	0.26	NA	−0.67	−0.49	Bedridden		16.7	Pneumonia
21	IIIB	F	12.3	6.1	Hyperactivity, unstable gait, hirsutism, and speech delay	0.01	NA	−2.84	−2.07	Wheelchair bound	12	13.9	Unknown
22	IIIB	M	14.9	2.7	Hirsutism, hyperactivity	0.01	369.8	−1.86	0.00	Walking	11		
23	IIIB	M	15.4	4.4	Speech delay, hyperactivity, and hirsutism	0	427.5	−1.82	−0.03	Walking			

TABLE 1 (Continued)

Patient No.	MPS type	Gender	Age (yr)	Age at diagnosis (yr)	Initial symptoms	Leukocyte specific enzyme activity[a]	Urinary GAG (μg/mg creatinine)[b]	Height (z score)	Weight (z score)	Ambulatory status	Age at the first seizure (yr)	Age at death (yr)	Cause of death
24	IIIB	F	17.1	5.2	Hyperactivity, hirsutism	0	97.6	−3.84	−1.36	Wheelchair bound			
25	IIIB	F	17.9	4.9	Hyperactivity, hirsutism	0.5	154.4	−2.69	−0.93	Wheelchair bound			
26	IIIB	M	18.2	6.0	Speech delay, hirsutism, and hyperactivity	0	346.1	−2.15	−0.61	Wheelchair bound	14		
27	IIIB	F	18.5	4.1	Speech delay, dysostosis multiplex	0	NA	−2.64	−3.16	Wheelchair bound			
28	IIIC	M	26.5	8.6	Speech delay, hyperactivity, and hirsutism	0.01	274.5	−1.85	−1.77	Wheelchair bound	20		
		Mean	10.1	4.7		0.1	422.3	−0.47	0.02		10.7	13.0	
		SD	5.7	2.1		0.1	290.3	1.97	1.49		4.8	3.0	
		Median	8.2	4.6		0.0	355.1	−0.2	0.0		11.0	13.0	

[a]Specific enzyme activity: MPS IIIA: heparan *N*-sulfatase, reference range: 4.1–12 nmol/17 hr/mg protein; MPS IIIB: alpha-*N*-acetylglucosaminidase, reference range: 1.4–5.4 nmol/hr/mg protein; MPS IIIC: acetyl CoA: alpha-glucosaminide acetyltransferase, reference range: 8.6–32 nmol/17 hr/mg protein.
[b]Reference values are age dependent: 1–3 years, 20.0–110.5; 3–5 years, 10.7–112.0; >5 years, 10.8–77.5.

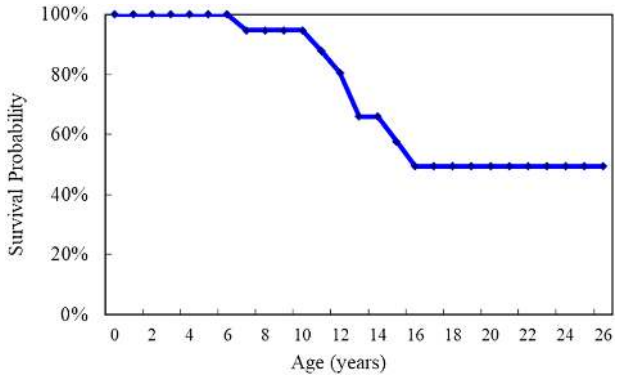

FIGURE 1 Kaplan–Meier Survival Curve for 28 patients with MPS III in Taiwan [Color figure can be viewed at wileyonlinelibrary.com]

Lee-Chen et al., 2002; 2002; Mangas et al., 2008; Tang et al., 2013; Weber et al., 1999). Two of them were missense mutations (p.L498P and p.A9E), two were splicing mutations (c.383 + 1G > T and c.764 + 1G > A), two were rearrangement mutations (c.999_1019dupCGT CTATGAGGCCATGACTGC and p.T332_T338dup7), and one was frameshift mutation (c.252_253ins19). In each case, 100 control chromosomes were screened for the existence of mutations and none was found.

4 | EEG

EEG assessment of 13 patients revealed eight (62%) with abnormal findings, including encephalopathy (n = 3), epileptogenicity (n = 3), and focal cortical dysfunction (n = 1).

4.1 | Brain MRI and CT

Eight patients had brain MRI or CT assessments performed to evaluate brain structure. All eight patients had various degrees of abnormalities, including cerebral atrophy (n = 5), hydrocephalus (n = 2), subdural effusion (n = 2), subdural hematoma (n = 1), and cerebellar atrophy (n = 1).

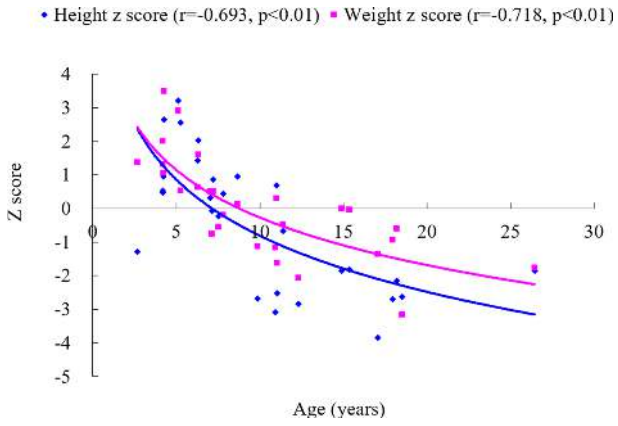

FIGURE 2 Age against SD scores (z scores) for height and weight of 28 patients with MPS III. The values of the two parameters both decreased with age (p < 0.05) [Color figure can be viewed at wileyonlinelibrary.com]

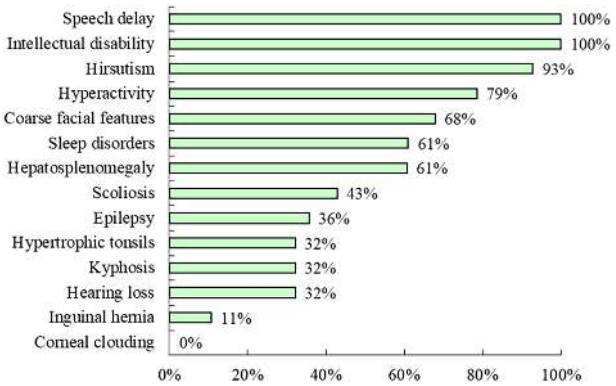

FIGURE 3 Clinical features of 28 patients with MPS III in Taiwan [Color figure can be viewed at wileyonlinelibrary.com]

4.2 | Airway assessment by laryngoscopy and bronchoscopy

Airway assessment by laryngoscopy and bronchoscopy of 10 patients revealed the presence of adenoid hyperplasia (n = 7), laryngomalacia (n = 6), tonsillar hyperplasia (n = 5), tongue hyperplasia (n = 3), velopharynx collapse (n = 3), redundant cuneiform cartilage (n = 1), vocal palsy (n = 1), and tracheomalacia (n = 1).

4.3 | ECG and echocardiography

ECGs in 10 patients revealed the presence of sinus arrhythmia (n = 3), sinus bradycardia (n = 2), and sinus tachycardia (n = 1). Echocardiographic examinations of 20 patients revealed 10 (50%) had valvular heart disease. Nine (45%) and three patients (15%) had valvular regurgitation or stenosis, respectively. The most prevalent cardiac valve abnormalities were tricuspid regurgitation (40%), followed by mitral regurgitation (15%), mitral stenosis (10%), aortic regurgitation (5%), and aortic stenosis (5%) (Figure 5). However, most patients with valvular heart disease had mild cases. Five (25%) and three patients (15%) had a thickened interventricular septum or mitral valve prolapse, respectively. The existence of valvular stenosis was positively correlated with increasing age (r = .688, p < .01).

4.4 | Hearing assessment by pure-tone audiometry and tympanometry

Six patients had hearing assessment by pure-tone audiometry. Mean value of air conduction (AC) of the better ear was 58.6 dB (reference range ≤ 25 dB). According to the WHO classification, all six patients

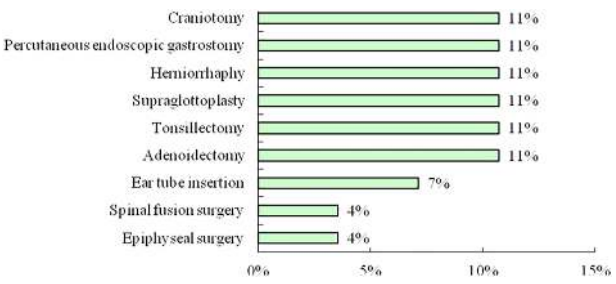

FIGURE 4 Types of surgical interventions for 28 patients with MPS III in Taiwan [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Mutational studies of 16 patients with MPS III in Taiwan

Patient No.	MPS type	Gender	Gene	Nucleotide[a]	Protein[b]	Location	Known / Novel
1	IIIB	M	*NAGLU*	[c.383 + 1G>T] + [c.1693C>T]	[-] + [p.R565W]	Intron 1 / Exon 6	N / K (Lee-Chen et al., 2002)
2	IIIB	M	*NAGLU*	[c.252_253ins19] + [c.1493T>C]	[-] + [p.L498P]	Exon 1 / Exon 6	N / N
5	IIIB	M	*NAGLU*	[c.999_1019dupCGTCTATGAGGCCATGACTGC] + [c.1081T>C]	[-] + [p.W361R]	Exon 5 / Exon 6	N / K (Tang et al., 2013)
6	IIIB	M	*NAGLU*	[c.926A>G] + [c.1241A>G]	[p.Y309C] + [p.H414R]	Exon 5 / Exon 6	K (Lee-Chen et al., 2002) / K (Weber et al., 1999)
7	IIIB	M	*NAGLU*	[c.383 + 1G>T] + [c.1693C>T]	[-] + [p.R565W]	Intron 1 / Exon 6	N / K (Lee-Chen et al., 2002)
10	IIIB	M	*NAGLU*	[c.660delC] + [c.1693C>T]	[-] + [p.R565W]	Exon 6 / Exon 6	K (Lee-Chen et al., 2002) / K (Lee-Chen et al., 2002)
12	IIIB	M	*NAGLU*	[c.26C>A] + [c.1004A>G]	[p.A9E] + [p.Y335C]	Exon 1 / Exon 5	N / K (Beesley et al., 2005)
13	IIIB	M	*NAGLU*	[c.764 + 1G>A] / Not detected	[-] / Not detected	Intron 4	N
14	IIIB	M	*NAGLU*	[c.700C>T] + [c.994_1014dup]	[p.R234C] + [p.T332_T338dup7]	Exon 4 / Exon 5	K (Mangas et al., 2008) / N
16	IIIA	M	*SGSH*	[c.126C>A] + [c.703G>A]	[p.N42K] + [p.D235N]	Exon 2 / Exon 6	K (Lee-Chen et al., 2002) / K (Lee-Chen et al., 2002)
17	IIIB	M	*NAGLU*	[c.461T>G] + [c.461T>G]	[p.I154R] + [p.I154R]	Exon 2 / Exon 2	K (Lee-Chen et al., 2002) / K (Lee-Chen et al., 2002)
19	IIIA	F	*SGSH*	[c.877C>T] + [c.1129C>T]	[p.P293S] + [p.R377C]	Exon 7 / Exon 8	K (Lee-Chen et al., 2002) / K (Lee-Chen et al., 2002)
20	IIIB	F	*NAGLU*	[c.1876C>T] + [c.1876C>T]	[p.R626X] + [p.R626X]	Exon 6 / Exon 6	K (Lee-Chen et al., 2002) / K (Lee-Chen et al., 2002)
22	IIIB	M	*NAGLU*	[c.388C>T] + [c.388C>T]	[p.R130C] + [p.R130C]	Exon 2 / Exon 2	K (Lee-Chen et al., 2002) / K (Lee-Chen et al., 2002)
26	IIIB	M	*NAGLU*	[c.388C>T] + [c.388C>T]	[p.R130C] + [p.R130C]	Exon 2 / Exon 2	K (Lee-Chen et al., 2002) / K (Lee-Chen et al., 2002)
27	IIIB	F	*NAGLU*	[c.1693C>T] + [c.1693C>T]	[p.R565W] + [p.R565W]	Exon 6 / Exon 6	K (Lee-Chen et al., 2002) / K (Lee-Chen et al., 2002)

Patients No.1 and No.7 are siblings. Patients No.22 and No.26 are siblings.
[a]Nucleotide: [allele 1] + [allele 2]
[b]Protein: [allele 1] + [allele 2]

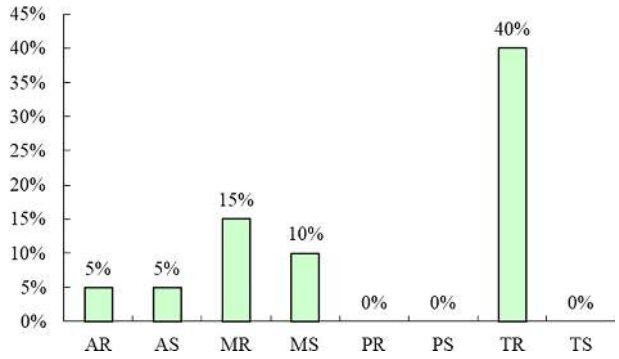

FIGURE 5 Incidence of cardiac valve abnormalities in 20 patients with MPS III in Taiwan. AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; MS, mitral stenosis; PR, pulmonary regurgitation; PS, pulmonary stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis [Color figure can be viewed at wileyonlinelibrary.com]

had various degrees of hearing loss (AC > 25 dB), including mild (AC 26–40 dB, *n* = 1), moderate (AC 41–60 dB, *n* = 1), and severe (AC 61–80 dB, *n* = 4). The type of hearing loss could not be identified in these patients due to unavailability of bone conduction data. Tympanograms resulted in classifications of type A (normal, *n* = 4) and type C (*n* = 2).

4.5 | Abdominal ultrasonography

Fourteen patients had abdominal ultrasonographic assessments performed to evaluate liver and spleen sizes. Eleven patients (79%) had hepatomegaly, and 10 (71%) had splenomegaly.

4.6 | BMD assessment by DXA

BMD evaluations by DXA were performed in three patients. After correction for height-for-age *z* score (HAZ) as previously described (Lin et al., 2013), HAZ adjusted BMD *z* score was −0.92, −0.65, and −5.03 for patient No. 24, No. 25, and No. 28, respectively. Patient No. 28 had osteoporosis (HAZ adjusted BMD *z* score < −2).

4.7 | Polysomnography

Three patients had overnight polysomnographic examinations to evaluate the sleep condition. OAHI was 3.4, 12.2, and 1.6 for patient No. 16, No. 17, and No. 18, respectively. All patients had some degree of obstructive sleep apnea, ranging from mild (OAHI 1.5–5, *n* = 2) to severe (OAHI >10, *n* = 1).

5 | DISCUSSION

This is the first report to describe the natural history, molecular and clinical characteristics of patients with MPS III in the Asian population. To the best of our knowledge, these were the only patients in Taiwan with a confirmed diagnosis of MPS III at the time of this study. The registry included patients with MPS III born from 1986 to 2013 with wide age heterogeneity and various clinical severity. Accurate knowledge of the natural course of the disease will help assess disease progression and therapeutic effects, as well as evaluate clinical and biomarker endpoints for clinical trials. The natural course and clinical manifestations of this disorder have been reported by several study groups in Caucasian populations (Buhrman et al., 2014; Delgadillo et al., 2013; Héron et al., 2011; Jansen et al., 2007; Malm & Månsson, 2010; Meyer et al., 2007; Ruijter et al., 2008; Truxal et al., 2016; Valstar et al., 2010; Velasco et al., 2017). Our results indicate that Taiwanese patients with MPS III manifest a broad spectrum of disease phenotypes from mild to severe, indicating the clinical heterogeneity of the disease.

Delgadillo et al., (2013) reported speech delay (85%), coarse facial features (78%), and hyperactivity (65%) were the most common symptoms before diagnosis for patients in Spain with MPS III (*n* = 55). Buhrman et al., (2014) described the most common initial symptoms for patients in the USA with MPS IIIA (*n* = 46) were speech/language delay (48%), followed by dysmorphology (22%) and hearing loss (20%). Consistent with these previous studies, the most common initial symptom in our cohort was speech delay (75%), followed by hirsutism (64%) and hyperactivity (54%).

Lavery, Hendriksz, and Jones (2017) reported the mean ages at death from 1977 to 2007 were 15.2, 18.9, and 23.4 years for patients in the UK with MPS IIIA (*n* = 84), MPS IIIB (*n* = 24), and MPS IIIC (*n* = 5), respectively. Delgadillo et al. (2013) reported the median age at death in patients in Spain with MPS IIIA (*n* = 9) was 15 years. The present study indicates the mean and median ages at death of patients with MPS III (*n* = 7) were both 13 years, similar to the results reported in the previous literature.

Information characterizing cause of death in MPS III is limited in the literature. In the report of Lavery et al. (2017), respiratory tract infections, notably pneumonia, is the leading cause of death in MPS IIIA (51%) and MPS IIIB (38%) patients. Delgadillo et al. (2013) reported cause of death as respiratory infection (60%) and cardiorespiratory failure (40%). In line with these findings, two out of three patients in our cohort with known causes of death died of pneumonia. Patients with neurological impairment more frequently suffer respiratory complications and experience more hospitalizations than those without neurological impairment (Havers et al., 2016). In addition, there are significant airway changes in the shape of the vocal cords and trachea in patients with MPS, which may be due to abnormal submucosal storage of GAG (Shih, Lee, Lin, Sheu, & Blickman, 2002).

Truxal et al. (2016) reported the mean age at confirmed diagnosis for MPS IIIA (*n* = 15) and MPS IIIB (*n* = 10) was 3.4 years. Delgadillo et al. (2013) reported the median ages at diagnosis in patients in Spain were 4.4, 3.1, and 6.3 years in MPS IIIA (*n* = 34), MPS IIIB (*n* = 11), and MPS IIIC (*n* = 10), respectively. In our patients, the median ages at confirmed diagnosis were 5.2, 4.4, and 8.6 years in MPS IIIA (*n* = 3), MPS IIIB (*n* = 24), and MPS IIIC (*n* = 1), respectively. Compared with these data, the age at confirmed diagnosis in our series was delayed about 1 to 2 years.

Delgadillo et al. (2013) reported 45% of patients with MPS III in Spain (*n* = 55) developed epilepsy at the median age of 8.7 years. In our cohort, 10 patients (36%) had epilepsy, and the median age at the first seizure was 11 years. EEG assessment revealed that 8 of the 13 patients (62%) had abnormal findings, including encephalopathy (*n* = 3), epileptogenicity (*n* = 3), brain atrophy (*n* = 3), subdural

effusion (*n* = 2), hydrocephalus (*n* = 1), and focal cortical dysfunction (*n* = 1). In our study subjects, all eight patients were identified with various degrees of brain structural abnormalities by brain MRI or CT, including cerebral atrophy (*n* = 5), hydrocephalus (*n* = 2), and subdural effusion (*n* = 2). Truxal et al. (2016) reported brain MRI revealed ventriculomegaly and loss of cortical volume in all subjects of MPS IIIA (*n* = 15) and MPS IIIB (*n* = 10). Our results were consistent with these findings.

Short stature in patients with MPS III is not as significant as that in other types of MPS, such as MPS IV, MPS VI, MPS I, and MPS II (Lin et al., 2013, Lin et al., 2014,2016). For these 28 patients, the mean *z* scores for height and weight were −0.47 ± 1.97 and 0.02 ± 1.49, respectively. However, 8 (29%) patients had striking short stature and 2 (7%) had significantly lower weight than normal for their age with a *z* score of < −2; most of these were older patients. Interestingly, before 8–10 years of age, most children with MPS III had positive height and weight *z* scores; however, after 10 years of age, most patients had negative height and weight *z* scores. The older patients had even lower *z* scores for height and weight, illustrating the progressive nature of the disease (Figure 2). Consistently, Buhrman et al. (2014) also concluded most MPS IIIA children (age range 0.9–13 years) had measurements above the 50th percentile for height and weight.

Coarse facial features with broad eyebrows, although frequently mild and easily missed, are detected in most patients with MPS III. The hair is usually dry and rough with hypertrichosis in most patients (Valstar et al., 2008). Delgadillo et al. (2013) reported the most prevalent symptoms before diagnosis were speech delay (85%), followed by coarse facial features (78%), hyperactivity (65%), recurrent diarrhea (50%), recurrent otitis (46%), sleep disorders (44%), hearing loss (30%), umbilical hernia (22%), and inguinal hernia (7%). Similarly, in our patients, the most prevalent clinical manifestations were speech delay (100%) and intellectual disability (100%), followed by hirsutism (93%), hyperactivity (79%), coarse facial features (68%), sleep disorders (61%), hepatosplenomegaly (61%), hypertrophic tonsils (32%), hearing loss (32%), and inguinal hernia (11%) (Figure 3). Delgadillo et al. (2013) reported orthopedic manifestations, such as scoliosis and kyphosis, were found in 50% of patients. Consistently, in our patients 43% had scoliosis and 32% had kyphosis.

Buhrman et al. (2014) described that 72% of patients with MPS IIIA underwent a tonsillectomy, adenoidectomy, or both. Delgadillo et al. (2013) reported 43% and 28% of patients in Spain had adenoidectomy or tonsillectomy, respectively, before diagnosis. In our cohort, 13 (46%) patients experienced at least one surgical procedure. The most prevalent surgical interventions were craniotomy (11%), percutaneous endoscopic gastrostomy (11%), herniorrhaphy (11%), supraglottoplasty (11%), tonsillectomy (11%), adenoidectomy (11%), ear tube insertion (7%), spinal fusion surgery (4%), and epiphyseal surgery (4%) (Figure 4). Three patients had received craniotomy at the time of this study, including Patients No. 4, No. 16, and No. 28. Patient No. 4 had car accident at 18 months of age with head injury and one episode of seizure, and craniotomy was performed. However, frontal bone defect developed 2 months later due to bone necrosis. Patient No. 16 received craniotomy for twice due to increased intracranial pressure and intracerebral hemorrhage at 5 years of age. Patient No. 28 had chronic subdural hematoma and underwent parietal craniotomy and removal of hematoma at 5 years of age.

The onset of dysphagia parallels the loss of motor milestones in patients with MPS III. Delgadillo et al. (2013) reported 29% of patients required gastric feeding buttons in their second decade of life which marked the late stage of the disease. Similarly, 3 (11%) of our patients received percutaneous endoscopic gastrostomy due to dysphagia.

Recurrent ear, nose, and throat infections are problems, especially in younger patients with MPS III. GAG is accumulated throughout the respiratory system. Respiratory function impairment is caused by multiple etiologies, including upper and lower airway obstruction, cervical myelopathy, chest wall restriction, skeletal dysplasia, and short stature. In our study, airway assessment by laryngoscopy and bronchoscopy of 10 patients revealed adenoid hyperplasia (*n* = 7), laryngomalacia (*n* = 6), tonsillar hyperplasia (*n* = 5), tongue hyperplasia (*n* = 3), velopharynx collapse (*n* = 3), redundant cuneiform cartilage (*n* = 1), vocal palsy (*n* = 1), and tracheomalacia (*n* = 1).

Cardiac involvement in MPS III is less common and milder compared with the other MPS types (Dangel 1998; Lin et al., 2014). Delgadillo et al. (2013) reported valvular disease detected in one patient and slight cardiomyopathy in four patients with MPS III. Consistently, echocardiographic examinations revealed that 45% and 15% of our patients had valvular regurgitation or stenosis, respectively. However, most patients with valvular heart disease had mild cases. Five (25%) and 3 (15%) patients had a thickened interventricular septum and mitral valve prolapse, respectively. The positive correlation between the presence of valvular stenosis and increasing age reinforces the concept of the progressive nature of cardiac disease.

There are multifactorial etiologies result in hearing loss in patients with MPS III. Conductive hearing loss is usually secondary to ossicle deformity, as well as recurrent serous otitis media and upper respiratory tract infection. GAG accumulation may attribute to sensorineural hearing loss (Lin et al., 2014). Buhrman et al. (2014) reported most of the hearing loss of patients with MPS IIIA in their study was sensorineural in origin by auditory brainstem response testing. However, audiometric testing is extremely difficult in patients with MPS III due to severe behavioral problems and intellectual disability. In our study, all six patients with available pure-tone audiometric assessment had various degrees of hearing loss. The type of hearing loss could not be identified in these patients due to unavailability of bone conduction data.

Truxal et al. (2016) reported abdominal MRI of patients with MPS IIIA and IIIB revealed increased liver and spleen volumes. We had similar results, with abdominal ultrasonographic assessments revealing 79% and 71% of patients had hepatomegaly and splenomegaly, respectively.

Because of malnutrition, a particularly small frame, an abnormal gait, and reduction of physical activities due to pain, exercise intolerance, or poor health condition, patients with MPS have an increased risk of poor bone mineralization (Lin et al., 2013). In our cohort, 1 of 3 (33%) patients had osteoporosis according to BMD assessment by DXA.

Obstructive sleep apnea, or sleep-disordered breathing, is a common disorder in patients with MPS (Lin et al., 2010). In our series, only

three patients with MPS III had overnight polysomnographic assessments, and all of them had some degree of obstructive sleep apnea.

In relation to the pathogenicity of the seven novel mutations identified in this study, the two missense mutations (p.L498P and p.A9E) are probably damaging to protein function and are predicted the pathogenicity according to bioinformatic programs, such as the PolyPhen-2prediction algorithm. Regarding to the pathological effects of the two splicing mutations (c.383 + 1G > T and c.764 + 1G > A), the cDNA is needed to be studied. Two rearrangement mutations (c.999_1019dupCG TCTATGAGGCCATGACTGC and p.T332_T338dup7) and one frameshift mutation (c.252_253ins19) are all assumed to cause disease because they are predicted to introduce the instability of the tertiary protein structure, followed by termination. In our cohort, molecular studies showed an allelic heterogeneity without clear genotype and phenotype correlations.

5.1 | Limitations

There are several limitations to this study. As a retrospective and multicenter study for this rare genetic disorder in Taiwan, there is a lack of complete molecular and clinical data for all enrolled subjects. The range of age and degree of disease severity were both quite wide. Due to differences in the number of patients and small sample size in each subtype, it was difficult to calculate comparative statistics. Therefore, larger cohort studies with a longer follow-up are warranted in the future.

6 | CONCLUSION

MPS IIIB is the most frequent subtype among MPS III in the Taiwanese population. This study demonstrated that MPS III had multisystemic dysfunction, including neurological, respiratory, cardiovascular, auditory, visceral, and skeletal systems. Consequently, a multidisciplinary approach to patient management is required once the diagnosis is made. Notably, the most common initial symptom was speech delay, hirsutism, and hyperactivity. These manifestations may help high-risk population screening for early diagnosis and potentially facilitate better treatment options. These findings and the follow-up data can be used to develop quality of care strategies and provide guidance for clinical trial endpoint evaluations.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DISCLOSURE OF INTERESTS

None.

AUTHOR CONTRIBUTORS

HYL performed data acquisition, statistical analyses, data interpretation, and drafted the manuscript. SPL participated in study design, data interpretation, and helped to draft the manuscript. CKC, CLL, RYT, YTL, YYF, and TLC performed biochemical analyses and revised the manuscript. PCC, DMN, FJT, WLH, SJL, and TMC were responsible for patient screening and revised the manuscript. All authors read and approved the manuscript.

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