Original Article

Developmental Outcomes after Rehabilitation in Pediatric Patients with Global Developmental Delay: A Retrospective Case-Control Study

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Objective: 1) To study developmental outcomes in patients with global developmental delay (GDD) following rehabilitation. 2) To study associated factors of developmental outcomes in patients with GDD following rehabilitation.

Materials and Methods: The present study was a retrospective descriptive study. GDD patients received rehabilitation program at the Thai Red Cross Rehabilitation Center between January 1, 2014 and December 31, 2019. Data were collected from medical records included demographic data, developmental quotient (DQ) calculated from Denver II, and associated factors determining developmental outcomes.

Results: There were 54 subjects at 29.7 months old in average. When comparing between before and after rehabilitation program, DQ in gross motor and personal-social domain improved significantly (p=0.002 and <0.001). Female gender (adjusted OR 13.66, p=0.005) and no history of chromosomal abnormalities (adjusted OR 3.49, p=0.048) were associated with DQ improvement in gross motor domain. Music therapy (adjusted OR 33.94, p=0.013), term delivery (adjusted OR 28.28, p=0.020), no history of seizure (adjusted OR 16.80, p=0.008), and program duration (adjusted OR 1.08, p=0.032) were associated with personal-social domain.

Conclusion: Following rehabilitation program, patients with GDD improved in gross motor and personal-social domain. Female gender and patients without history of chromosomal abnormalities revealed association with gross motor improvement. In addition, patients without history of seizure, music therapy, term delivery, and program duration were associated with personal-social improvement.

Keywords: Global developmental delay; Pediatric rehabilitation; Denver II; Developmental quotient

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Children younger than five years old are in the important steps of their lives due to the dynamic changes of their growth and development. It is the most effective period for developmental stimulation[1]. The World Health Organization (WHO) reports 15% to 20% of all children in the world have developmental problems, with 95% being found in low-to-moderate socioeconomic countries[2]. The definition of global developmental delay (GDD) is a significant delay in two or more from five developmental domains. The developmental domains are gross motor and fine motor, expressive language, receptive language, and social/adaptive behaviors. This definition can be applied to children younger than five years of age[3-6]. Tools are used to evaluate child development. One of the tools commonly used for the screening of child developmental delay is Denver II. Paula's study in 2011 reported the sensitivity of Denver II tool was 56% to 83% and specificity of 43% to 80%[7]. Denver II tool evaluates four domains, gross motor, fine motor, language, and personal or social domains. The result from Denver II tool corrected with age will become developmental quotient (DQ). DQ represents quality of development by its percentage of normal development of child of the same age[8].

There are studies that used DQ as a parameter indicating children development corrected with age. For example, DQ was used to determine effects of copy number variations (CNV) on developmental aspects of developmental delayed children in study by Park et al, 2019[9]. This paper reported that DQ of gross motor domain in children diagnosed with

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CNV was significantly lower than children without CNV. Another study from Liu et al in 2018 reported improvement of DQ after receiving Portage Guide to Early Education (PGEE) program, which included variety of games as early interventions that aim to enhance the development of various skills in children with GDD[10].

Regarding factors that determined rehabilitation outcome, Gabriels et al study in 2001 examined factors that predict developmental outcome in children diagnosed with autism. The study showed that treatment intensity and type, family stress factors, and intelligence ability affected outcome following rehabilitation[11].

In 2014, Thomaidis et al conducted a prospective observational study to determine predictors of severity and outcome of GDD children. They found that prematurity and intrauterine growth restriction (IUGR) were significantly related to severity of GDD. Furthermore, poor developmental outcomes were associated with IUGR, low socioeconomic status, and non-compliance to rehabilitation plan[12].

The authors' rehabilitation center serves as an outpatient pediatric rehabilitation service. Between 2014 and 2019, 256 new patients visited the authors' rehabilitation center. The percentage of patients diagnosed as GDD in 2014 were 23.05% in the authors' service. This number increased to 31.11% in 2019. Denver II tool was used as a screening tool to evaluate and follow-up development of patients. There is no research about rehabilitation outcomes and factors determining outcomes in the authors' rehabilitation center. Thus, the research team developed this six-year retrospective study.

Objective

Primary objective

The primary objective was to study developmental outcomes in pediatric patients with GDD following rehabilitation in four domains as gross motor, fine motor, language, and personal or social domains. Outcomes were recorded by Denver II test and as DQ.

Secondary objective

The secondary objective was to study associated factors of developmental outcomes in pediatric patients with GDD following rehabilitation.

Materials and Methods

Ethical consideration

Ethics approval obtained by the Institutional Review Board (IRB) of Faculty of Medicine, Chulalongkorn University, IRB Number 782/63.

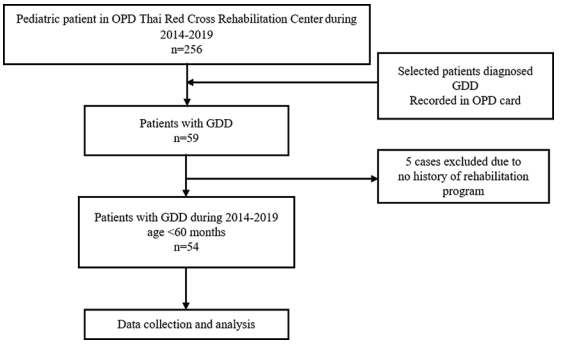

Figure 1. Flow chart.

Research methodology

Research design: The present study was a retrospective descriptive study.

Target population: Pediatric patients diagnosed with GDD who received outpatient pediatric rehabilitation at Thai Red Cross Rehabilitation Center between January 2014 and December 2019. Fifty-nine 59 patients participated as illustrated in study flow chart (Figure 1).

Inclusion criteria:

1. Diagnosed as GDD as shown in medical records.
2. History of receiving outpatient pediatric rehabilitation at Thai Red Cross Rehabilitation Center between January 1, 2014 and December 31, 2019.
3. Age at the first treatment session less than five years old.
4. Denver II developmental assessment were recorded.

Exclusion criteria:

1. Other diagnoses, for example cerebral palsy, autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD).

Procedure

First, the researcher team reviewed the medical records from the outpatient pediatric rehabilitation at Thai Red Cross Rehabilitation Center according to inclusion and exclusion criteria. The collected data from the medical records included baseline characteristics, mode of delivery, birth weight[13], gestational age, gender, age, underlying disease, social history including care giver, hometown, education level, history of previous treatment, and compliance of rehabilitation treatment. Good compliance[14] means attended rehabilitation treatment at least 80% of the rehabilitation plan.

The primary outcome was DQ collected at two time point. The first one was DQ before the first session of rehabilitation (DQ1) and the other was DQ after the last rehabilitation sessions (DQ2). DQ was calculated by developmental age (DA) divided by chronological age (CA) and multiplied by 100 (DQ = DA/CA×100). There were two secondary outcomes, DQ improvement and DQ difference value. DQ improvement defines as DQ2 greater than DQ1 while not-improve means DQ2 equal or less than DQ1. There were factors used in Univariate analysis and multivariate analysis including patient factors such as gender, age, mode of delivery, birth weight, brain abnormality/seizure, and chromosome abnormalities, and treatment factors such as duration of treatment, compliance, and history of receiving music therapy.

Data and statistical analysis

Stata, version 11 (StataCorp LP, College Station, TX, USA) was used for data analysis. Data were expressed in percent, mean (standard deviation, SD) and median (interquartile range, IQR). The Wilcoxon signed rank test was used to compare the DQ between before and after rehabilitation due to non-normal distribution. Univariate analysis and multivariate analysis were used to analyze the factors associated with the developmental outcomes and expressed by crude odds ratio (OR) and adjusted OR with 95% confidence interval (CI), respectively. A p-value of less than or equal to 0.05 was considered as statistically significant.

Results

Between 2014 and 2019, there were 55 from 59 patients diagnosed with GDD that received outpatient pediatric rehabilitation at Thai Red Cross Rehabilitation Center. Baseline characteristics and demographic data are showed in Table 1. There were 21 female patients (38.9%) and 33 male patients (61.1%). The average age was 29.7 months old. Eighty-five-percent of all patients received physical therapy, while 90.7% received occupational therapy. Furthermore, 45% and 33.3% received speech therapy and music therapy, respectively. In addition, 74.1% of all patients had good compliance with the treatment.

In terms of severity, if DQ score was less than 35, this would be graded as severe GDD. Moderate, mild, borderline, normal were account for DQ score of 35 to 50, 50 to 70, 70 to 90, and more than 90, respectively(15). The present study found that 68.5% of patients were graded as severe gross motor delay. Additionally, 61.1%, 59.3%, and 81.4% of patients were severe in each domain of fine motor, language, and personal-social domain (as shown in Figure 2).

Table 1. Demographic data of participants

	n (%)
Age (month); mean±SD	29.7±14.9
Program duration (month); median (IQR)	13 (5.75 to 28.75)
Sex (n=54)	
Female	21 (38.9)
Male	33 (61.1)
Chromosomal/genetic disease (n=54)	
No	31 (57.4)
Yes	23 (42.6)
Seizure or abnormal brain imaging (n=54)	
No	38 (70.4)
Yes	16 (29.6)
Gestational age (n=53)	
Preterm	7 (13.3)
Term	46 (86.7)
Birth weight (n=52)	
<2,500 g	13 (25.0)
2,500 to 3,500 g	39 (75.0)
Delivery (n=54)	
Normal labor	46 (85.2)
Cesarean section	8 (14.8)
Compliance (n=54)	
Poor	14 (25.9)
Good	40 (74.1)
PT program (n=54)	
No	8 (14.8)
Yes	46 (85.2)
OT program (n=54)	
No	5 (9.3)
Yes	49 (90.7)
Speech therapy (n=54)	
No	9 (16.7)
Yes	45 (83.3)
Music therapy (n=54)	
No	36 (66.7)
Yes	18 (33.3)

SD=standard deviation; IQR=interquartile range; PT=physical therapy; OT=occupational therapy

Table 2 shows DQ of the four developmental domains in comparison between before and after rehabilitation program.

Table 3 and 4 reports factors associated DQ improvement of each domain.

Table 3 reports that female gender is significantly associated with gross motor domain development (crude OR 8.94, p=0.008) and when analyzed by multivariate analysis, it was found that female gender

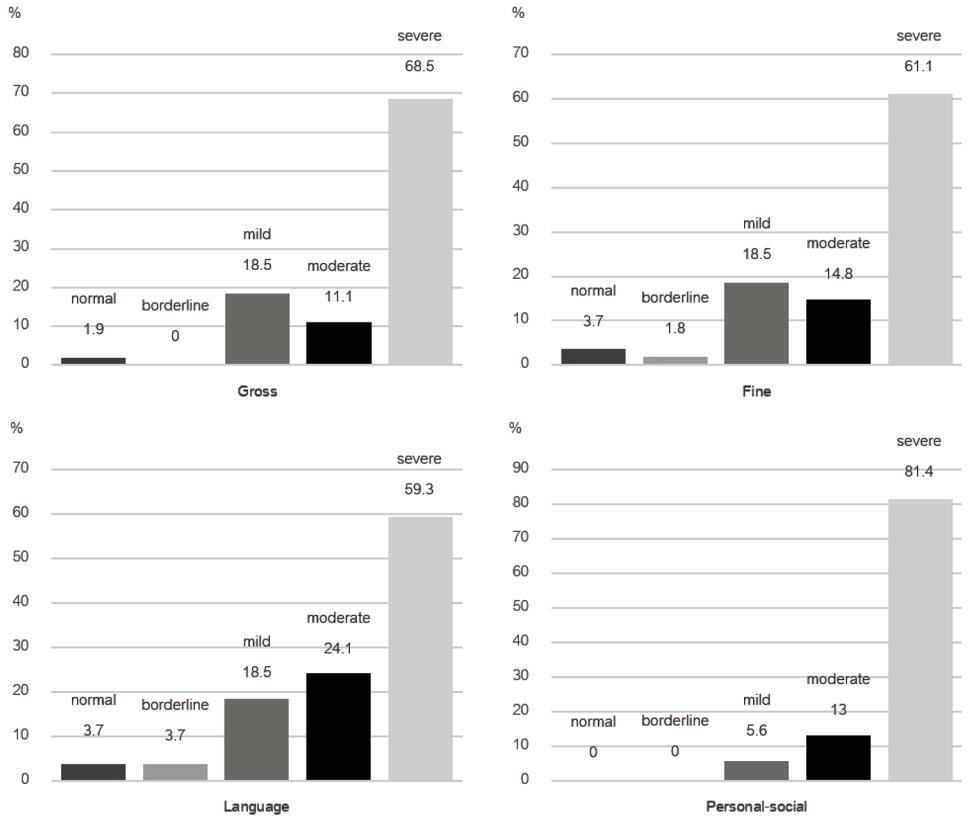

Figure 2. DQ severity.

Table 2. Comparison of DQ score in 4 developmental domains between before program and after the last program

Domain	DQ before program (n=54); median (IQR)	DQ after the last program (n=54); median (IQR)	p-value
Gross motor	29.00 (19.00 to 42.00)	36.00 (19.00 to 57.00)	0.002*
Fine motor	31.00 (17.00 to 48.00)	30.50 (18.00 to 48.00)	0.233
Language	27.00 (17.00 to 46.00)	26.00 (17.00 to 50.00)	0.685
Personal-social	18.50 (10.00 to 32.00)	29.50 (17.00 to 50.00)	<0.001*

DQ=development quotient; IQR=interquartile range

Wilcoxon signed rank test (* statistic significant at p<0.05)

and patients without chromosome abnormalities were statistically significantly associated with better outcomes in gross motor domain (adjusted OR 13.66, p=0.005 and adjusted OR 5.76, p=0.024), respectively. There were no significant associated factors found in both fine motor and language domains.

According to univariate logistic analysis, Table 4 shows that patients without history of seizure or abnormal brain imaging and patients received music therapy were associated with better outcome in personal-social domain (crude OR 3.75, p=0.039 and crude OR 12.14, p=0.021), respectively. Furthermore, patients without history of seizure or abnormal brain imaging (adjusted OR 16.80, p=0.008), patients who received music therapy (adjusted OR 33.94, p=0.013), patients with history of full-term delivery (adjusted OR 28.28, p=0.020), and duration of program (adjusted OR 1.08, p=0.032) were associated factors of personal-social domain by using multivariate analysis.

In aspect of DQ difference value, data showed that only in personal-social domain that patients with history of receiving music therapy were associated with significant improvement in DQ difference value (p=0.009).

Discussion

Children with GDD that underwent rehabilitation

Table 3. Factors associated to DQ improvement: gross motor domain

	Improve	No improve	Crude OR[a] (95% CI)	p-value	Adjusted OR[b] (95% CI)	p-value
Birth weight (n=52); n (%)						
<2,500 g	8 (61.5)	5 (38.5)	0.74 (0.19 to 2.74)	0.65		
2,500 to 4,000 g	26 (66.7)	13 (33.3)				
Sex (n=54); n (%)						
Female	19 (90.5)	2 (9.5)	8.94 (1.79 to 44.69)	0.008*	13.66 (2.19 to 84.90)	0.005*
Male	17 (51.5)	16 (48.5)				
Seizure/abnormal brain imaging (n=54); n (%)						
Yes	14 (87.5)	2 (12.5)				
No	22 (57.9)	16 (42.1)	0.45 (0.12 to 1.64)	0.227		
Chromosomal disease (n=54); n (%)						
Yes	12 (52.2)	11 (47.8)				
No	24 (77.4)	7 (22.6)	3.14 (0.97 to 10.17)	0.056	5.76 (1.25 to 26.47)	0.024*
Compliance (n=54); n (%)						
Good	28 (70.0)	12 (30.0)	1.75 (0.49 to 6.14)	0.383		
Poor	8 (57.1)	6 (42.9)				
Received music therapy (n=54); n (%)						
Yes	10 (55.6)	8 (44.4)	0.48 (0.15 to 1.57)	0.224		
No	26 (72.2)	10 (27.8)				
Delivery (n=48); n (%)						
Normal labor	11 (52.4)	10 (47.6)	0.38 (0.11 to 1.29)	0.123		
Cesarean section	20 (74.1)	7 (25.9)				
Gestational age (n=53); n (%)						
Term	30 (65.2)	16 (34.8)	0.75 (0.13 to 4.31)	0.747		
Preterm	5 (71.4)	2 (28.6)				
Age (month); mean±SD	29.22±14.34 (n=36)	30.5±16.04 (n=18)	0.99 (0.96 to 1.03)	0.763		
Duration of program (month); median (IQR)	11 (5 to 24) (n=36)	17.5 (8 to 34) (n=18)	0.97 (0.94 to 1.01)	0.145		

SD=standard deviation; IQR=interquartile range; OR=odds ratio; CI=confidence interval

Binary logistic regression (* statistic significant at p<0.05)

[a] Univariate logistic regression; [b] Multivariate logistic regression

program at the authors' rehabilitation center between 2014 and 2019 counted as 23.05%. In present study center, patients were mostly classified as severe degree in four out of five domains, which were gross motor domain, fine motor domain, language, and personal-social domain, at 68.6%, 61.1%, 59.3%, and 81.4%, respectively. The severity of disease was not consistent with the study from Wasant et al[15]. They studied the Factors influencing development of Down syndrome children that included mild degree patients together with a study from children hospital in Greece from Thomaidis et al[12]. One of the reasons to explain this finding was the present study center had affiliation with a tertiary hospital and a medical school.

DQ comparison between before and after rehabilitation program found only gross motor and personal-social domain showed significant improvement. This finding seems to be due to Denver II, which is a tool that more suitable with overall developmental evaluation than specific domain evaluation. Thus, Denver II alone may not be delicate enough to evaluate and follow-up in fine motor and language domain evaluation.

In aspect of gross motor and personal-social domain, DQ median improves 4 and 5.5 points, respectively after 13 months of training. Thomaidis et al[12] research was conducted in 142 patients with GDD without definitive etiology. After two years, they found that DQ average improved 10.4 points. Furthermore Liu et al study[10] in patients that received the PGEE program also found that DQ average improved by about 10 points. There are two reasons to explain the lower improvement in the present study. First, baseline DQ of the present study patients is

Table 4. Factors associated to DQ improvement: personal-social domain

	Improve	No improve	Crude OR[a] (95% CI)	p-value	Adjusted OR[b] (95% CI)	p-value
Birth weight (n=52); n (%)						
<2,500 g	10 (76.9)	3 (23.1)	1.36 (0.31 to 5.89)	0.683		
2,500 to 4,000 g	27 (69.2)	12 (30.8)				
Sex (n=54); n (%)						
Female	13 (61.9)	8 (38.1)	0.52 (0.16 to 1.70)	0.28		
Male	25 (75.8)	8 (24.2)				
Seizure/abnormal brain imaging (n=54); n (%)						
Yes	8 (50)	8 (50)				
No	30 (78.9)	8 (21.1)	3.75 (1.07 to 13.12)	0.039*	16.80 (2.07 to 136.05)	0.008*
Chromosomal disease (n=54); n (%)						
Yes	19 (82.6)	4 (17.4)				
No	19 (61.3)	12 (38.7)	0.33 (0.09 to 1.22)	0.097		
Compliance (n=54); n (%)						
Good	30 (75.0)	10 (25.0)	2.25 (0.63 to 8.07)	0.214		
Poor	8 (57.1)	6 (42.9)				
Received music therapy (n=54); n (%)						
Yes	17 (94.4)	1 (5.6)	12.14 (1.45 to 101.45)	0.021*	33.94 (2.08 to 553.67)	0.013*
No	21 (58.3)	15 (41.7)				
Delivery (n=48); n (%)						
Normal labor	16 (76.2)	5 (23.8)	1.88 (0.53 to 6.72)	0.330		
Cesarean section	17 (63.0)	10 (37)				
Gestational age (n=53); n (%)						
Term	33 (71.7)	13 (22.3)	1.90 (0.37 to 9.70)	0.438	28.28 (1.70 to 496.46)	0.020*
Preterm	4 (57.1)	3 (42.9)				
Age (month); mean±SD	29.21±14.40 (n=38)	30.69±16.11 (n=16)	0.99 (0.95 to 1.03)	0.735		
Duration of program (month); median (IQR)	16 (10 to 31) (n=38)	6 (3 to 20.5) (n=16)	1.05 (0.99 to 1.10)	0.065	1.08 (1.01 to 1.16)	0.032*

SD=standard deviation; IQR=interquartile range; OR=odds ratio; CI=confidence interval

Binary logistic regression (* statistic significant at p<0.05)

[a] Univariate logistic regression; [b] Multivariate logistic regression

lower than the other two studies due to severe degree of GDD. Second, the training duration of patients in Thomaidis et al research[12] was more than twice from the present study.

Associated factors that affected developmental improvement

History of seizure or abnormal brain imaging: According to the present study, patients without history of seizure or without abnormal brain imaging have 16 times of personal-social domain improvement. These findings are similar with Hong et al study[16] that reported that patients without seizure had better opportunities in rehabilitation outcomes with statistical significance. Furthermore, Chen et al study[17] reported that 80% of pediatric patients with GDD were associated with brain abnormalities, and neurological and musculoskeletal system. Therefore, the present researchers suggested that comprehensive history taking, and further neurological investigation are crucial in patients with GDD.

Chromosomal or genetic disease: The present study found that patients without chromosomal or genetic disease had opportunities to have better development in gross motor domain five times more than patients with chromosomal or genetic disease. According to previous studies[4,6,17], GDD is between 28% to 47% to be caused from chromosome abnormalities or genetic disease. From all the above data, further investigation about genetic cause is recommended in patients with GDD with unknown cause.

Gender: In the present study, there were 33 male and 21 female or 61.1% and 38.9%. This is

similar to other studies[12,17] that mostly reported that male gender seems to have developmental delay condition more often than female. In the authors' opinion, the reason to support is x-link chromosome abnormalities caused GDD condition. According to the present studies, female gender is associated with good prognosis in gross motor domain calculated as 13 times of male gender. This study corresponded with the study of Epir and Yalaz[18] that evaluated Turkish children aged two weeks to six years old, by Denver tool. That study revealed female gender seemed to have better development in gross motor domain than male gender. By contrast, the study of Hong et al[16] reported that gender was not associated with gross motor outcome after training in cerebral palsy or GDD patients. Further research about correlation between gender and developmental outcomes after training is recommended.

History of receiving music therapy: The study revealed that patients who received music therapy were associated with better outcomes in personal-social domain calculated as 34 times more than not receive music therapy. Furthermore, music therapy is also associated with more DQ difference value when compared between before and after training. In the present study rehabilitation center, the authors have provided group music therapy that encourage the rehabilitation program and improve communication skills for the patients. This is supported by the study from Barbara that found that group music therapy improved social skills for children with moderate intellectual disability. Moreover, Nicholson et al study[19] and Yang study[20] reported music therapy improve communication skill, social skill, behavior, and child-parent relationship in patients with GDD. Li study[21] supported that music therapy increase quality of life for patients with developmental disabilities.

Other associated factors: Based on Thomaidis et al study[12], negative factors related outcome following rehabilitation are preterm delivery, low birth weight, birth asphyxia, low socioeconomic status, and poor compliance. In the other hand, term delivery and duration of rehabilitation are the only two factors that associated with personal- social domain improvement according to the present study.

Unfortunately, the present study cannot support the compliance of rehabilitation program is significantly related to developmental improvement. While considering Table 3 and 4, good compliance groups trend to have better outcome in each domain without statistical significance. Larger sample size may lead to statistical significance.

In aspect of the measurement tool, the present research used DQ that calculated from Denver II corrected by age. DQ has been published by studies about child development recently[9,22,23]. As mentioned above, Denver II is more appropriate with overall developmental evaluation than specific domain. Glascoe et al study[24] reported that Denver II was suitable as a screening tool because sensitivity is about 83% with 43% of specificity. Correspondingly with supporting evidence from Ryu and Sim's study, they reported that Denver II has better sensitivity and better yield as screening test in patient with language developmental delay[25]. Additionally, Denver II has reliability at 0.99 with standard deviation of 0.016. In the authors' opinion, Denver II is one of the practical tools for evaluation before rehabilitation program. Moreover, another specific tool is suggested to use together with Denver II to evaluate each particular domain.

There are limitations of the present study. First, retrospective chart review may lead to lack of complete data and variety of assessors. Second, the present study was a descriptive study. Third, data were collected from only one setting and small sample size. Prospective study with appropriate measurement tool in each domain is recommended in the future.

Conclusion

According to the present retrospective study, patients with GDD attending out-patient rehabilitation had significant improvement in gross motor and personal-social domain. Female gender and patients without history of chromosome abnormalities are associated with gross motor domain improvement. Factors associated with better outcomes of personal-social domain are patients that received music therapy, patients without history of seizure or abnormal brain imaging, patients with history of full-term delivery, and longer duration of rehabilitation. Therefore, rehabilitation practice for children with GDD may be more beneficial with music therapy. Lastly, complete history taking, and further neurological and genetic investigation are crucial in patients with GDD with unknown cause.

What is already known on this topic?

GDD is a significant delay in two or more from five developmental domains, which include gross motor, fine motor, expressive language, receptive language, and social/adaptive behavior domains.

Denver II is commonly used for the screening of child developmental delay. DQ stands for quality of

development by its percentage of normal development of child of the same age. There are associated factors that determined rehabilitation outcome of children with GDD.

What this study adds?

In aspect of GDD patients, factors associated with better outcomes following rehabilitation of personal-social domain are patients who receive music therapy, patients without history of seizure or abnormal brain imaging, patients with history of full-term delivery, and longer duration of rehabilitation. Therefore, complete history taking, and further neurological and genetic investigation are beneficial in patients with GDD with unknown cause.

Female gender and patients without history of chromosome abnormalities are associated with gross motor domain improvement in children with GDD.

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Conflicts of interest

All authors declare no conflict of interest regarding the publication of the research.

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