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ASSESSMENT OF MOTOR FUNCTION OF CHILDREN WITH DOWN SYNDROME: A CLINICAL STUDY

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Abstract: The study aimed to assess the gross motor function of children with Down syndrome (DS) and its relationship with factors capable of influencing its development. A cross-sectional clinical study with an assessment of gross motor function (GMFM-88) was conducted at the Genetic Pediatrics service in Botucatu/SP, 2018 to 2020. Were included 44 children with DS aged five months and incomplete ten years old. The results shows that the child's age at suspicion or in the diagnosis of DS, age at start of motor stimulation, and the age at the beginning of the diagnosis of hypothyroidism were significantly associated in the GMFM-8 ($P<0.05$), positively correlated with better score of motor function, as well as the number of weekly stimulation consultations in the first year of life. In conclusion, it is essential to start motor stimulation as early as possible, as well as the timely treatment of hypothyroidism, so prevalent in these children.
Keywords: Down syndrome, Children, Motor function.

INTRODUCTION

Down syndrome (DS) is a genetic disorder characterized by the presence and expression of three copies of chromosome 21 in about 90% to 95% of cases. Mosaicism (46,XY/47,XY + 21 or 46,XX/47,XX + 21) is a rare form of Down syndrome and is responsible for only 1% of the predominance among those who have this disorder, while translocation accounts for approximately 4% of DS cases, being Robertsonian t (14;21) (14q;21q) the most usual (Kim et al., 2010; National Down Syndrome Society, 2020). DS is the most common chromosomal abnormality in humans (Balkan *et al*., 2010; Thillainathan *et al*., 2015) and the most frequent cause of developmental disabilities in the population (Harris and Shea,2021; Mourato *et al*.,2014).

Approximately one in 700 babies in the United States is born with DS. Similarly, in Brazil it is estimated that for every 700 births there is one case of trisomy 21, representing about 300 thousand people with the syndrome, regardless of ethnicity, gender or social class (National Down Syndrome Society, 2020).

Children with DS also have delays in the development of motor function as a result of associated impairments, including muscle hypotonia, joint hyperextensibility, delayed acquisition of postural control and poor balance (Russel *et al.,*1998). Additionally, they are also more prone to have dysfunction of thyroid hormones (8 to 49%), including congenital or acquired hypothyroidism and hyperthyroidism (Pierce *et al*., 2017). The decrease in the production of thyroid hormones and the increased serum dosage of thyroid-stimulating hormone (TSH) is frequent from the neonatal period to puberty, with risk of 1% of congenital hypothyroidism and 14% or more of hypothyroidism acquired along their lives (Niegawa *et al*., 2017), Sociedade Brasileira de Pediatria,2020).

The early diagnosis of thyroid disorders is beneficial to the physical, psychomotor and intellectual development of children with DS. Thus, it is necessary to evaluate the thyroid function with serum measurement of the TSH and free tetraiodothyronine (free T4) hormones at birth through newborn screening tests carried out at six and 12 months of age, and annually until early adulthood (Sociedade Brasileira de Pediatria,2020).

In clinical practice, it is challenging to distinguish signs and symptoms of DS from signs related to overt hypothyroidism as they sometimes overlap with similar characteristics, such as feeding difficulties, decreased physical activity and hypotonia. Untreated hypothyroidism can, therefore, aggravate manifestations already associated with DS during childhood, such as psychomotor development, somatic growth and intellectual retardation (Pierce *et al*., 2017).

The follow-up by a multidisciplinary team and the overall care of children with DS, as well as the degree of stimulation to which these children are exposed and the environment in which they are inserted, are essential for their growth and motor development (Chaves and Almeida, 2018; Kim et al., 2017). In children with DS, motor development is particular and associated with the syndrome's own characteristics, such as hypotonia and brain damage resulting from extra chromosome 21, factors that cause delayed psychomotor development and learning (Malak *et al*., 2015). On the other hand, like every child they have the potential to develop psychomotricity due to the wide neuroplasticity that can be stimulated from the first months of life (Yamauchi *et al.,* 2019; Bull, 2020).

Gross Motor Function Measure (GMFM) (Russel *et al.,*1998) is a scale capable of measuring gross motor function in static and dynamic quantitative aspects (Houwen *et al*., 2009; Salavati *et al*., 2014; 2015) that has been commonly used by researchers (Chrysagis *et al*., 2012; Scholtes *et al*., 2010). This scale was validated to assess motor function in children with DS between 5 months and 16 years of age (Russel *et al.,*1998), a population known to be more prone to delays in this domain (Trindade and Nascimento, 2016; Watson-Scales et al., 2018). It was also validated and translated for use in Brazil (Almeida *et al*., 2016).

Therefore, this study is justified by the high frequency of thyroid disorders, especially primary hypothyroidism, and the few studies on factors that can interfere with the motor development of children with DS, such as age at DS diagnosis, age at start of thyroid dysfunction and age at start of motor stimulation, in addition to the comorbidities associated with DS and hospitalizations.

The aim of the present study was to assess the gross motor function of children with DS and its relationship with factors capable of influencing its.

METHODS

This research is a cross-sectional clinical study with data collection through questionnaire and clinical assessment of gross motor function using the Gross Motor Function Measure Scale (GMFM-88). It was carried out between August 2018 and February 2020 at the Genetic Pediatrics service of the Botucatu Clinics Hospital (HCFMB), São Paulo, Brazil.

In this study, a convenience sample of 44 children of both genders aged five months to incomplete ten years and with a medical diagnosis of DS, all confirmed by the karyotype test, was included. The idea was to exclude children who had two attempts of motor assessment by the proposed scale, but that could not be performed due to the difficulty of acceptance by the child of the activities proposed for scale validation, including crying, irritability, sleep and refusal to participate in the activities. However, there was no exclusion, since nobody fit this profile.

DATA COLLECTION

A questionnaire was applied to the people responsible for the child, and the data were collected through the patient's electronic record at HCFMB.

The data collection involved: maternal data and birth conditions; birth and current diseases; hospitalizations; child's age at the time of diagnostic suspicion and confirmation of DS; age at start of motor stimulation and specialized therapy consultations in the first year of life; variation or not in the value of thyroid-stimulating hormone (TSH) in the serum and/or newborn screening test, and if existing, whether the child is being treated with levothyroxine (LT4),considering hypothyroidism the main thyroid dysfunction presented by the participants in the study.

The GMFM-88 scale was applied by a physiotherapist with experience in the use of this instrument. The results were plotted in specific protocols of the scale and differentiated according to the age group. The assessment was carried out at the same moment of the interview in an office at the Genetic Pediatrics outpatient clinic of the Botucatu Clinics Hospital (HCFMB), and when it was not possible to perform the assessment in one visit, another one was scheduled.

GROSS MOTOR FUNCTION MEASURE-88 (GMFM-88)

The GMFM-88 consists of motor functions grouped into 5 dimensions: 1) GMFM-88 A: lying and rolling (17 items); 2) GMFM-88 B: sitting (20 items); 3) GMFM-88 C: crawling and kneeling (14 items); 4) GMFM-88 D: standing (13); and lastly 5) GMFM-88 E: walking, running and jumping (24 items) (Russel *et al.*,2002). According to the GMFM-88 guidelines formulated for the assessment of children with DS, the environment should be as familiar for the children as possible to encourage the performance of activities (Russel *et al.*, 2002).

It is assumed that a 5-year-old child will be able to perform 100% of the proposed activities of the GMFM (i.e. obtain "3 points" in all 88 items). The score "0" (child does not start the activity) was differentiated from the items that are not tested (NT) (Russel *et al.*, 2002; 2015).

The scores for the GMFM-88 items were summed to calculate the gross scores and percentages for each of the five dimensions, as well as the total score.

As the score is an uncategorized variable, for a better visualization of the values they

were classified into quartiles. Considering that there is no normal distribution nor cut-off point for the definition of adequate or inadequate, these quartiles were divided as follows: Q1 <38%; Q2 38 to 74%; Q3 75 to 95%; and Q4> 95%.

THYROID FUNCTION

All participants were classified according to thyroid function into euthyroidism, hypothyroidism or hyperthyroidism through the serum results of TSH and free T4 (free thyroxine circulating in the blood), following the criteria of Brazilian Society of Pediatrics (2020): participants with serum TSH levels above 10 micrograms per deciliter (μg/dl) and free T4 above 4.0 μg/dl were considered hypothyroid; participants with an increased serum TSH level above 10 μg/dl and a normal serum free T4 level were considered to have subclinical hypothyroidism; participants with both TSH and free T4 values within normal limits were considered euthyroid. Didn't have any participants with suppressed TSH values (below the lower limit of normality in the reference value) with an increase in free T4 above the upper value of normality were considered hyperthyroid.

In order to make a better statistical analysis, the classification used was: dysfunction and euthyroidism. For those with dysfunction, they were divided into hypothyroidism and subclinical hypothyroidism.

DATA ANALYSIS

The data were analyzed using SAS software, version 9.4.Chi-square test or Fisher's exact test was used for associations between the categorized variables and the quartiles of the motor function score. Student's t-test was used to compare the means. For means with more than two categories, the ANOVA analysis followed by the Tukey test were applied.

The Pearson's correlation was obtained between continuous variables and the motor function assessment score in a linear regression model adjusted between age, age at start of stimulation and motor function score. P-value less than 0.05 was considered statistically significant.

This study received approval from the Botucatu Medical School Research Ethics Committee (92025018.4.0000.5411/2018). Written informed consent was obtained from all participants' caregivers.

RESULTS

The mean age of the participants in the study was 35.0 months, ranging from 3 to 106 months. According to the results, there was a slight predominance of females (56%) and participants from other municipalities belonging to the Regional Health Department of Bauru (DRS-VI), where the Botucatu Clinics Hospital acts as secondary and tertiary references in assistance (76%). Mothers were the majority of caregivers interviewed (92%), among which 52% were between 20 and 40 years old when they gave birth to their child and 14% were over 40 years old. A total of 34.1%t of the children were preterm newborns and 47.7% presented low birth weight.

Current disease was reported in 75% of the participants, among which 19.4% had heart disease, such as atrial septal defect and total atrioventricular septal defect with cardiac surgery in the first year of life. Among the other diseases found, 26.5% refer to thyroid disease, 6.1% to heart and thyroid diseases and 24.5% to other diseases, such as gastroesophageal reflux and wheezing.

Twenty-two children (72.7%) were hospitalized in the first year of life, being the main reasons pneumonia or respiratory conditions (17 children, 38.6%).

The diagnostic suspicion of Down syndrome at birth occurred in 70% of the

participants (being only 6% with antenatal diagnosis), and the confirmation through karyotype test happened in the first year of life for 70% of them and in the first quarter of life for 24%. Thus, the timely stimulation for the motor development of these children started with a mean of nine months, ranging from one to 60 months, with a mean of 1.4 consultations per week in the first year of life (ranging from 1.2 to 5 times).

Regarding the assessment of thyroid function, 11.4% of children (n = 5) had a newborn screening test altered to primary hypothyroidism. In the follow-up evolution, 38.6% of those included in the study (n = 17) showed changes in the serum TSH level, among which 16 (94.1%) received replacement of thyroid hormone with levothyroxine (LT4). The mean age at start of hormone replacement with LT4 was less than 1 month.

For the assessment of motor function, the scores were obtained in percentage values and subdivided into quartiles, being 70% the value for mean performance. Among children over 5 years old, the nine included in the study did not reach 100% of the scale score, being only one (11.1%), an euthyroid children, classified in the second quartile (Q2), and eight (88.9%) in the fourth quartile (Q4), being only one with hypothyroidism child.

With increasing age, there was an increase in the motor function score of children, represented by the high percentage observed in the last quartiles and according to the analysis of the mean test scores obtained. There was no significant relationship between motor function and gender, origin, child's age or maternal education (Table 1). The median GMFM-88 score was 64% (22%-99%) for girls and 64% (19%-99.0%) for boys, representing no significant difference in either group according to gender (p=0.96).

MOTOR FUNCTION AND THYROID DISORDERS

Table 2 shows that there was no association between motor function and diagnosis of thyroid function through tests performed on the participants, as well as in relation to the drug treatment recommended in cases of dysfunctions.

It is important to mention analyzing the table 2, that the thyroid function of children with DS, the hypothyroidism was present in 38% of them, being mostly acquired (62.5%), and all of them required treatment with thyroid hormone replacement, levothyroxine sodium (LT4).

In table 3 and Graph 1 were observed that child's age (p <0.01), age at start of motor stimulation (p = <0.01) and start of early timely treatment of hypothyroidism (0.04) were correlated with the trend of higher GMFM-88 score during the participants' assessment.

By analyzing the correlations between continuous variables and GMFM-88 score, it was possible to note a statistical significance in the relationship between age at start of motor stimulation and age at diagnostic suspicion and confirmation (p value 0.03 and 0.01, respectively), number of weekly consultations for stimulation in the first year of life (p value 0.02), child's age (p value 0.01) and GMFM-88 score (p value <0.01). The age at start of treatment with levothyroxine after the diagnosis of hypothyroidism showed a remarkable correlation with the number of weekly consultations for motor stimulation in the first year of life (p value 0.0351), the length of hospitalization at birth (p value 0.03) and the GMFM-88 score (p value 0.04), shows in table 3.

Variable	Q1*		Q2*		Q3*		Q4*		P
	N	%	N	%	N	%	N	%	
Gender									
Female	8	66.7	4	36.4	8	46.2	4	44.5	0.54
Male	4	33.3	7	63.6	4	53.8	5	55.5	
Age group									
≤ 1 year old	6	50.0	6	46.2	0	0.00	0	0.00	**<0.01**
1 to 3 years old	6	50.0	4	30.8	5	45.4	1	16.7	
3 to 5 years old	0	0.00	0	0.00	5	45.4	1	16.7	
> 5 years old	0	0.00	3	23.10	1	9.2	4	66.6	
Origin									
Botucatu	1	8.3	1	8.3	4	50.0	3	25.0	0.08
Other municipalities*	11	91.7	11	91,7	4	50.0	9	75.0	
Maternal age at birth									
< 20 years old	2	16.7	2	15.4	1	8.3	0	0.00	0.34
20 to 30 years old	2	18.10	1	7.7	3	25.0	6	46.2	
30 to 40 years old	6	50.0	7	53.8	8	66.7	5	45.5	
> 40 years old	2	16.7	3	23.1	0	0.00	1	8.3	
Maternal education									
Incomplete primary school	3	25.0	3	30.0	2	22.2	3	25.0	0.98
Complete primary school	1	8.3	0	0.00	1	11.2	1	8.3	
Incomplete high school	2	16.7	3	30.0	2	22.2	3	25.0	
Complete high school	5	41.7	2	20.0	2	22.2	3	25.0	
Higher education	1	8.3	2	20.0	2	22.2	2	16.6	

(Quartiles: Q1 < 0.38 | Q2 0.38-0.74 | Q3 0.75-0.95 | Q4 > 0.95).

* Municipalities belonging to the Regional Health Department of Bauru (DRS VI).

Table 1. Association between quartiles of GMFM-88 score and demographic characteristics.

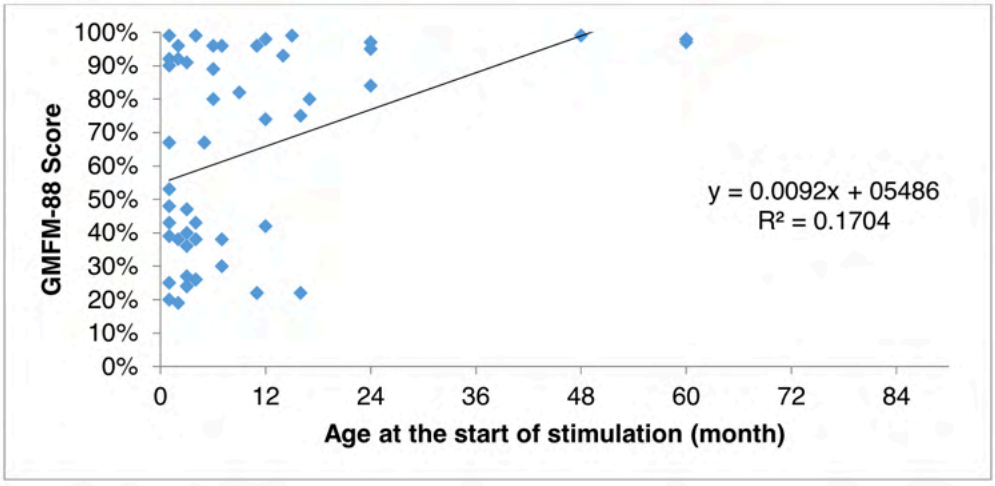
Variable	Q1*		Q2*		Q3*		Q4*		P
	n	%	n	%	n	%	n	%	
Heel-stick test									
Normal	9	81.8	11	84.6	10	90.9	13	100.0	0.49
Altered	2	18.2	2	15.4	1	9.1	0	0.00	
Serum TSH									
Normal	8	66.7	6	54.5	6	50.0	7	77.8	0.83
Altered	4	33.3	5	45.5	6	50.0	2	22.2	
Replacement with levothyroxine									
Yes	4	33.3	4	36.4	6	50.0	2	22.2	0.86
No	8	66.7	7	63.6	3	50.0	7	77.8	
Diagnosis of thyroid function									
Euthyroidism	8	66.7	7	63.6	6	50.0	7	77.8	0.19
Hypothyroidism	4	33.3	4	36.4	6	50.0	2	22.2	

*(Quartiles: Q1 < 0.38 | Q2 0.38-0.775 | Q3 0.775-0.94 | Q4 > 0.94).

Table 2. Association between quartiles of GMFM-88 score and thyroid function.

Variable	GMFM-88 score	P
Child's age	0.66667	**<0.01**
Age at diagnostic suspicion	0.33682	0.06
Age at diagnostic confirmation	0.24937	0.13
Age at start of professional stimulation	0.41278	**<0.01**
Number of consultations/week with therapist in the 1st year of life	0.00616	0.96
Length of hospitalization at birth	0.13624	0.41
Number of hospitalizations in the 1st year of life	0.15323	0.28
Age at start of thyroid dysfunction treatment	0.23862	**0.04**

Table 3. Pearson's correlation between variables with GMFM-88 score.



Graph 1. Correlation between Gross Motor Function Measure-88 score and age at start of stimulation.

DISCUSSION

The results of this study indicate that the diagnosis of DS as early as possible with the subsequent start of multidisciplinary follow-up and regular motor stimulation in an attempt to anticipate the difficulties inherent to the syndrome itself and promote a timely intervention has a positive impact on the gross motor function score of these children, thus contributing to a better overview of their overall evolution over the years.

It is known that children with Down syndrome tend to have developmental delays in relation to their peers who do not have the syndrome (Malak *et al*., 2015). Pioneering studies have shown that children with DS have greater difficulties in developing motor skills than those without DS (Carr, 1970; Merlyn and White, 1973). Other studies report that 6-year-old children with DS do not develop functions typical of 5-year-old *children with normal function development (Russel et al.,1998; Connolly* et al., 1993). The difference regarding the development of motor skills increases with age and is approximately 2 years in 5-year old children with DS (Russel *et al.,*1998).

Even so, the degree of developmental delay due to DS varies widely during childhood, and an ideal early intervention can allow the acquisition of appropriate developmental skills (Niegawa *et al*., 2017). Additionally, these delays are also affected by pathophysiologic processes and the shape and volume of the brain, especially the cerebellum, caused by the additional chromosome 21 (Pinter *et al*., 2001).

Based on the obtained results, it is our intention to stimulate knowledge, practices and the perception that the development of children with DS should be the focus of actions that favor it, controlling possible situations that interfere with their full development within the limitation generated by the presence of the extra chromosome 21. For this purpose, knowledge on factors that positively and negatively interfere with the motor function of these children is relevant. We also intend to promote improvements in the prevention and treatment of thyroid disorders in the follow-up of these children, taking into account their impact on the health care of children.

Therefore, despite the fact that this study focuses on the assessment of motor function as one of the sectors of child development, other works in the literature established that gross motor skills such as sitting and walking are associated with receptive language in both typically (He *et al*., 2015; Libertus and Violi, 2016) and atypically developing children (Yamauchi *et al.,* 2019; Walle, 2016; LeBarton and Landa, 2019). Similarly, Moore *et al.* (2019) discovered that gross motor skills such as crawling and walking are associated with expressive language, while other studies on typically and atypically developing children did not report such correlation (Belmonte *et al*., 2013; Dadgar *et al*., 2017; Kim 2008).

The prevalence of the hypothyroidism in the children of this study is in agreement with those found in the literature in this population (Pierce *et al*., 2017; Niegawa *et al*.,2019).

The stimulation of children with DS should be provided as early as possible so that the opportunities for interaction with the environment, the motor responses close to the normal pattern and the learning capacity are increasingly greater, taking advantage of brain neuroplasticity to activate and promote brain structures (Yamauchi *et al.,* 2019; Ismail *et al*., 2017). The increased interest in such researches is leading to new knowledge on the windows of vulnerability that increase the feasibility of actions oriented to children with Down syndrome.

Furthermore, we believe in the interrelationship between the domains

of human development, being the motor function inserted in the physical domain and closely related to the cognitive and personal-social domains. Thus, considering the target of optimal functionality of the individuals in their community, special attention should be given to motor function of these children so as to stimulate the acquisition of such skills as a contributor to the acquisition of other skills that are essential to their quality of life and social and educational insertions.

However, it is worth mentioning that our study presented some limitations. The first constraint was the reduced size of the sample, since there may be other correlations with GMFM-88 not identified in children with DS that could be possibly observed with a larger number of participants. Finally, as the study refers to a well-structured Genetic Pediatrics service for diagnosis confirmation from the follow-up of children with DS, as well as for the diagnosis and treatment of thyroid disorders and the start of motor stimulation, the results presented herein may not reflect the reality of other services with less readiness and technology for this practice and assistance.

CONCLUSION

The diagnostic suspicion and confirmation of DS favored the start of motor stimulation in the first year of life, positively influencing the improvement in the gross motor function of these children with increasing age, as well as the start of timely treatment of hypothyroidism. Therefore, the results suggest that the incorporation of technologies for early diagnosis and the proposal of correct therapeutic treatments are essential for the motor development of these children.

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DECLARATION OF CONFLICTING INTERESTS

The authors certify that there is no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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