



## Intensive Neuromotor Therapy improves motor skills of children with Cornelia de Lange Syndrome: case report

*Terapia Intensiva Neuromotora melhora as habilidades motoras da criança com Síndrome de Cornélia de Lange: relato de caso*

*El cuidado intensivo neuromotor mejora las habilidades motoras de los niños con síndrome de Cornelia de Lange: reporte de caso*

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### Abstract

**Introduction:** The Cornelia de Lange Syndrome (CdLS) is a rare genetic syndrome. Children with CdLS usually require physical therapy, however the efficacy of physical therapy intervention in this population is lacking in the research literature. **Objective:** The aim of this study was to report the effect of Intensive Neuromotor Therapy (INMT) on gross motor function and participation of a child with CdLS using the International Classification of Functioning, Disabilities and Health (ICF) model. **Method:** A Brazilian child with CdLS was followed for over seven months while undergoing three modules of INMT. **Results:** The child demonstrated an evolution of gross motor function with gains of 11.28% in the first module, 9.22% in the second module, and 10.29% in the third module of INMT. **Conclusion:** INMT resulted in improvements in

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gross motor function and participation during daily activities in a child with CdLS. Further studies of larger cohorts are needed to investigate the efficacy of INMT in children with CdLS.

**Keywords:** Cornelia de Lange Syndrome. Physical Therapy. Motor Skills.

### Resumo

**Introdução:** A síndrome de Cornelia de Lange (SCL) é uma síndrome genética rara. Crianças com SCL geralmente necessitam de fisioterapia, porém a eficácia da intervenção fisioterapêutica nessa população é escassa na literatura científica. **Objetivo:** O objetivo deste estudo foi relatar o efeito da Terapia Neuromotora Intensiva (TNMI) sobre a função motora grossa e participação de uma criança com SCL usando o modelo de Classificação Internacional de Funcionalidades, Incapacidades e Saúde (CIF). **Método:** Uma criança brasileira com SCL foi acompanhada durante sete meses, enquanto submetida a três módulos de TNMI. **Resultados:** A criança demonstrou uma evolução da função motora grossa com ganhos de 11,28% no primeiro módulo, 9,22% no segundo módulo e 10,29% no terceiro módulo do TNMI. **Conclusão:** a TNMI resultou em melhorias na função motora grossa e participação durante as atividades diárias em uma criança com SCL. São necessários mais estudos de coortes para investigar a eficácia do TNMI em crianças com SCL.

**Palavras-chave:** Síndrome de Cornélia de Lange. Fisioterapia. Habilidade Motora.

### Resumen

**Introducción:** El síndrome de Cornelia de Lange (SCL) es un síndrome genético raro. Los niños con SCL por lo general requieren fisioterapia, sin embargo, es escasa en la literatura científica la eficacia de esta intervención en este público. **Objetivo:** Informar el efecto de la terapia neuromotora intensiva (TNMI) en la función motora gruesa y la participación de un niño con SCL mediante el modelo de Clasificación Internacional de Funcionamiento, Discapacidades y Salud (CIF). **Método:** Se puso en seguimiento a un niño brasileño con SCL durante siete meses mientras se sometía a tres módulos de TNMI. **Resultados:** El niño demostró una evolución de la función motora gruesa con ganancias de un 11,28% en el primer módulo, de un 9,22% en el segundo y de un 10,29% en el tercer módulo de TNMI. **Conclusión:** La TNMI presentó mejoras en la función motora gruesa y en la participación durante las actividades diarias en un niño con SCL. Se necesitan futuras investigaciones adicionales de cohortes para investigar la eficacia de TNMI en niños con SCL.

**Palabras clave:** Síndrome de Cornelia de Lange. Fisioterapia. Habilidades Motoras.

## Introduction

The Cornelia de Lange Syndrome (CdLS) was first described in 1916. The first publication was dated from 1933, in Holland [1]. CdLS is considered as a rare genetic development syndrome [2], affecting 0.5 to 0.6 for each 100.000 born [1], without distinction of race. This syndrome is more prevalent in female with a proportion of 3:1 [3].

The most accepted etiology is the autosomal recessive genetic origin through the gene mutation. Regarding to genetic alterations, there are 5 genes

commonly identified as causative (NIPBL, RAD21, SMC3, a hemizyous pathogenic variant in HDAC8 or SMC1A), with NIPBL (Nipped B gene Like) being the most common [4, 5], even some studies showing normal karyotype [6], which leads to the possibility of several phenotypic manifestations.

The CdLS may cause variable phenotypic such as delay on growth and neuromotor development, distinctive facial features (microbrachycephaly), low hair implantation, wider and joined eyebrows, hypertrichosis, small nose, thin lips and micrognathia. Other alterations less frequent are malformation of

hands (syndactyly), agenesis, cardiopathies, skeletal, visual and digestive alterations, which demonstrate the complexity of the case [2, 3].

Most of CdLS children present intellectual impairments [3] from moderate to severe [7]. Some of them also have behavioral alteration “including aggressive, self-injurious, mood disturbance, and autistic-like traits” [5].

The diagnosis is made through these phenotypic features associated with growth and motor skills development analysis. In CdLS is also expected impairments in the voluntary movement [8]. In the neurological rehabilitation area, to identify these aspects is not easy. Children with CdLS were recommended to have a multidisciplinary intervention [9, 10]. Two studies regarding CdLS [1, 6] describe clinical and genetic aspects, with no report of physical therapy for these cases.

The International Classification of Functioning, Disabilities and Health (ICF) [11, 12] recommend the Gross Motor Function Measure (GMFM) for evaluating motor function and daily activities [13] in children with neuromotor disorders [5].

For children with neurological disorders, physical therapy with intensive protocols can be an alternative to increase results [14]. In this sense, the Intensive Neuromotor Therapy (INMT) [15, 16] is a modular training composed of 2-3h/day of physical activities, 5 times a week, during 4 weeks, with rest or maintenance periods between modules. The INMT can use orthotic garments or suit wear which offers movement resistance, and the therapy can be done in an Ability Unit of Exercise (AUE) using bungee cords to provide sensory stimulation, movement through resistance, standing posture and balance strategies [17] during the therapy. Most of the previous studies were performed with cerebral palsy children [14], but positive effects in gross motor skills were also showed in Down syndrome [18] and in spinal amyotrophy [19].

Thus, the aim of this study was to report the effect of Intensive Neuromotor Therapy on gross motor function, and participation in daily activities of a child with Cornelia de Lange Syndrome using the International Classification of Functioning, Disabilities and Health model.

## Methods

This study can be characterized as a case report, which used retrospective analyses of records from a

child with CdLS. This investigation was approved by the Research Ethics Committee from the Brazilian Institute of Therapies and Teaching (Ibrate) registered under number 1.429.717, clinical registration RBR-2st594. The INMT was performed in a Center of Rehabilitation, in Curitiba, Paraná, Brazil, with the parents' consent.

## History

The history was collected in the first evaluation, and the parents responded an informal interview with information about health, daily and education activities.

The mother at 35 years of age presented: hypertension, obesity and risk pregnancy. The child was born on 03/11/2013 with 30 weeks gestational age, showing fetal distress. At birth, weight was 1,060 kg and 34 cm of height. The child remained in the intensive care unit (ICU) for nearly five months. The child had a CdLS diagnosis considering some signals: microcephaly, malformations of the upper limbs, medial axial slit in the hand associated with syndactyly, delay of motor skills development. He feeds through gastrostomy (fundoplication performed at 3 months) and he had undergone surgery for testicular hernia repair (left) and excision of a sebaceous cyst. Because of it, he started to use the following drugs: phenobarbital, amlodipine, enalapril, furosemide, protovita plus vitamin D and cephalixin .

In a chest X-ray, he had report as “Rising Heart”, later confirmed as cardiac malformation (Ebstein's anomaly) by echocardiography. The child presents normal axial and appendicular muscle tone, and facial hypertonia. The fusion of the posterior arch of T11, L5 e S1 and shortening of the vertebral body of T11 was observed in an anteroposterior spine X-ray. At the beginning of INMT, he was 2 years-old, 12.0 kg, 79 cm.

## Evaluation

The gross motor function was assessed by the same therapist using the Gross Motor Function Measure (GMFM-88). The GMFM-88 quantifies motor aspects through 88 items scored from 0 to 3 [13] and consists in a motor function evaluation by ICF domains [11, 12]. The physiotherapist who evaluated the child was the same therapist who did the interventions, and has experience. The GMFM-88 was applied in a single day, inside a large and comfortable room with the floor

covered by acetate-vinyl ethylene (EVA). The child wore comfortable clothes that allowed full mobility and the room kept temperature from 22 °C to 24 °C.

Parents were asked (always at beginning and at the end of each module) to respond about functional improvement of the child on daily activities and mobility by their observation to verify some ICF domains of participation in others activities not included on GMFM-88 [20]. Parents should answer the questions: “Did you note any difference in your son’s during daily activities? What kind of difference? In which activity?”.

### Intervention description

The child completed three modules of INMT (each module: 2h hours a day, 5 days a week, during 4 weeks = 40h in total) in 7 months, (1<sup>st</sup> in May, 2<sup>nd</sup> in September and 3<sup>rd</sup> in November, with interspersing periods of maintenance (4 weeks = 16h in total). Each period of maintenance was composed by 2 hours a day of physical therapy, twice a week (June, July, August and October). “Maintenance” are periods between two modules in which the child had less hours of intervention when compared to INMT protocol.

The INMT protocol includes the *PediaSuit™*, *TheraSuit™*, *Bobath* and the Conventional kinesiotherapy. The INMT terminology is recently used by Neves et al. [15, 16], which presents a protocol of intensive physical therapy during 2-3 hours a day,

5 days a week, during 4 weeks, with individual goals identified by GMFM-88 and a professional experience evaluation. This workload is established according to the main diagnosis. Normally CP and Down syndrome children often do 3 hours a day and children with neurodegenerative diagnosis perform 2 hours a day. In this case report, considering child age and to avoid fatigue, the protocol used 2 hours a day, with rest breaks and fluids intake.

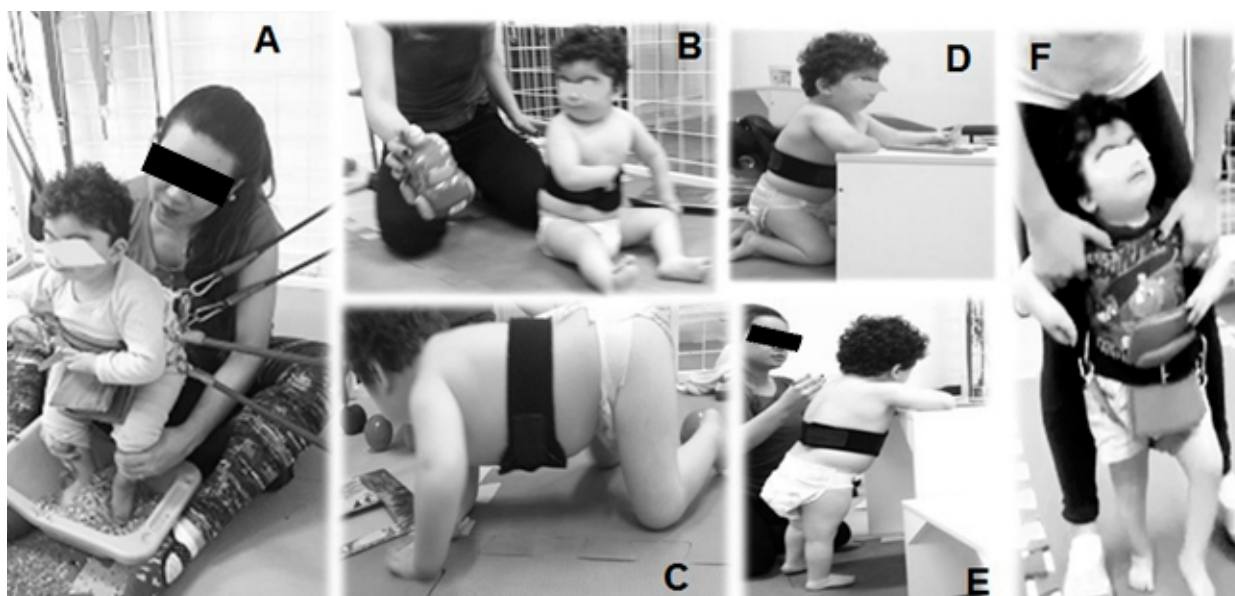
The INMT protocol was composed of: (a) warm up (massages and/or brushing, stretching); (b) endurance exercise in the AUE called Monkey and/or functional activities; (c) exercises with the suit wear from *PediaSuit™* in an AUE called Spider with bungee cords; (d) Respiratory exercises when necessary; (e) Gait training [15, 17]. The gait training is possible even for children without independent walking, like the child from this report due to the suit wear and bungee cords that could provide support. All therapies were conducted by a physical therapist with experience with this protocol.

All intervention procedures were planned based on task-oriented activities (Table 1) exemplified in Figure 1.

Data analyses were carried out using descriptive statistics to compare pre (initial) and post (final) GMFM-88 scores in five dimensions (A to E), due to lack of reference values of motor skills for children with CdLS.

**Table 1** – Goals and intervention procedures on INMT protocol for children with CdLS (Curitiba, Brazil, 2015)

Intended goals	Procedural interventions task-oriented activities
Sensorial stimulation	Various textures stimulation: box with rice, sago, play dough, soft glove, brush, temperature variations.
To promote stretching of upper and lower extremities	Passive manual stretching;
To promote global strengthening with focus in lower limbs	Functional strengthening by postural transfers
To promote scapular and pelvic mobilization	
To improve static and dynamic balance	Different exercises with bungee cords, balls, rolls, balance board in the AUE
To improve control trunk To stimulate postural transfers	Movement facilitation to transfer from sit to 4 points by different ways and surface
To stimulate orthostatism To favor gait phases and suspend gait training	Mobile AUE for gait training on treadmill with weight support and speed variation (during: 15 a 20 minutes), gait facilitation by physiotherapist.



Note: A: Activities of sensorial stimulation; B: incentive to sit and transfer; C: 4 points training and crawling; D: kneeling to stand training; E: stand position; F: gait training.

**Figure 1** – Examples of activities during the Intensive Neuromotor Therapy (INMT – Curitiba, Brazil, 2015).

## Results

At the end of INMT, the child was with 2 years and 7 months, 12.8 kg and 81 cm. The initial and final

data evaluation was presented in Table 2. Results show an evolution of the gross motor function with gains of 11.28% in the 1<sup>st</sup> module, 9.22% in the 2<sup>nd</sup> module, and 10.29% in the 3<sup>rd</sup> module.

**Table 2** – Initial and final GMFM-88 evaluation from a child with CdLS (Curitiba, Brazil, 2015)

	Moment	A (lying and rolling)	B (sitting)	C (crawling and kneeling)	D (standing)	E (walking, running and jumping)	Total GMFM-88	Goal areas
May	M1 Initial	50.98%	26.67%	0.00%	0.00%	0.00%	15.53%	38.82%
	M1 Final	82.35%	48.33%	2.38%	0.00%	0.00%	26.61%	44.35%
	M1 Difference	31.37%	21.66%	2.38%	0.00%	0.00%	11.28%	18.47%
September	M1 Initial	86.27%	33.33%	28.57%	0.00%	0.00%	29.64%	49.39%
	M1 Final	98.04%	51.67%	38.10%	5.13%	1.39%	38.86%	38.86%
	M1 Difference	11.77%	18.34%	9.53%	5.13%	1.39%	9.22%	9.23%
November	M1 Initial	90.20%	43.33%	21.43%	2.56%	0.00%	31.50%	39.38%
	M1 Final	98.04%	58.33%	50.00%	2.56%	0.00%	41.79%	52.23%
	M1 Difference	7.84%	15.00%	28.57%	0.00%	0.00%	10.29%	12.85%
	<b>Total Difference (M3Final- M1Initial)</b>	47.06%	31.66%	50.00%	2.56%	0.00%	26.26%	13.41%

Note: M = module.

Table 2 shows a total gain (after three modules of INMT) of 47.06 % in the dimension A (lying and rolling) and 50% in dimension C (crawling and kneeling). It is also evident that the gains occurred progressively module-by-module, with higher gains in the 1<sup>st</sup> module in the dimension A (31.37%), in the 2<sup>nd</sup> module greater gains in dimension B (18.34%) and 3<sup>rd</sup> module greater gains in dimension C (28.57%) which was also the dimension with higher scores in absolute terms, comparing the difference of the three assessed modules.

It can also be observed that the periods between the intensive modules in which the “Maintenance” was carried out for the beginning of a new module demonstrate a drop of punctuation especially in the dimension B and C. This happened both from the 1<sup>st</sup> to the 2<sup>nd</sup> module in which the “Maintenance” period was 3 months, and from the 2<sup>nd</sup> to the 3<sup>th</sup>

in which the interval for a new module was only 1 month.

Since the end of first module, the mother reported the improvement in performance of keeping postures (for mobility domain of ICF). This information was reported again, always at the end of the INMT modules. Initially the mother reported that the patient remained most of the time lying, even to play, but after three INMT modules, he has adopted the sitting posture for longer periods, which facilitate the environment exploration and the use of arms. Therefore, the INMT can be considered a good tool for motor skills gains because it has made the child play at home with better motor function.

During the seven months of intervention, the patient showed improvements in components of the ICF, motor function, noted by the scores of GMFM, and participation in daily activities cited by the mother’s report (Figure 2).

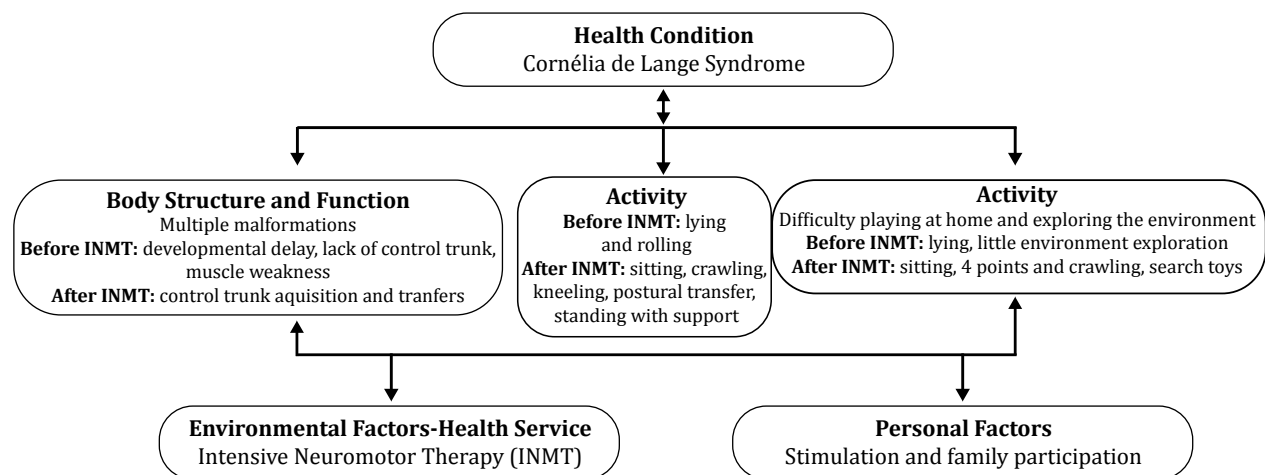


Figure 2 – Principal results of Intensive Neuromotor Therapy (INMT) by ICF model.

## Discussion

Considering CdLS as a rare syndrome and poorly described in terms of possibilities of intervention, physical therapy is an option for a child with neuromotor disorders caused by this syndrome [9]. The literature suggests that high-intensity exercises, as proposed by INMT, with an approach that emphasizes task-oriented activities, with specific goals, are the best way to provide a better learning experience in therapy for daily activities [21, 22] confirmed by the results of this case report.

The patient presented larger quantitative gains, in the total score, after the 1<sup>st</sup> module (18.47%). However, when analyzing in terms of complexity of the tasks, it was observed that the gain in the 1<sup>st</sup> module is mostly related to the supine position (dimension A: 31.37%). Probably this gain was the basis for the gains observed in the seated position (dimension B: 18.34%) in the 2<sup>nd</sup> module and to crawling and kneeling (dimension C: 28.57%) in the 3<sup>rd</sup> module.

The child had difficulty in trunk control at the beginning of INMT, which was an intended goal of

the intervention, especially in antigravity postures. Thus, the acquisition of sitting position (dimension B) represents the first step towards gains in antigravity postures [23]. This gain in control trunk has already been described by authors [15, 16] in children with cerebral palsy (CP) and spinal amyotrophy (SA), respectively. Although in this study no scale of fine motor skills or motor functions related to hands were used. However, considering patient hands malformations due to CdLS, it is possible to suggest that the patient gained manual skills because the sitting postural maintenance is strongly associated with an increase of manual skills [24].

The largest gains observed in the dimension C at the end of the 3<sup>rd</sup> module related to crawling and kneeling skills show that intervention favored trunk control as well as it allowed to get this posture starting from the sitting posture. This could be explained by the use of the cage ("Monkey" or "Spider") with bungee cords promoting trunk stabilization, with consequent simplification of movements. At the same time, it stimulates the sensory afferents, which would act to stimulate neural connections and allow a better match of tone, body symmetry, would favor the acquisition of motor milestones, improve balance, muscle strength and motor coordination [14]. In addition, dimension C is the key to the acquisition of active environmental exploration [23].

For a long time the sitting posture and crawling were considered distinct marks. Currently there is evidence [23] that these two important marks are closely related, allowing greater exploitation of the environment therefore stimulating development, just as the transition of these positions offers the child experience of change to new skill gains [23]. It was observed a tendency to significant gains in these two functional marks progressively in this study, and probably the intensive training, with variability of stimulus offered in support of a common goal seems to promote the motor functions acquisition. Stimulus variability has been described as the key for development and allows acquisitions and motor skills transfer [25]. For the purpose of trunk control, for example, different positions were planned in the cage in a playful manner, and the patient was encouraged in complex functional tasks, such as walking on treadmill, in supported and facilitated manner.

The exercise of walking on treadmill was another factor that may have spurred gains in the dimensions C

(crawling and kneeling), considering the opportunity to practice the triple flexion patterns, in suspension on treadmill, with verbal stimulus from the physical therapists, reaching complex movements [26] and providing transfer of learning from therapy to the daily activities of the child [21].

Although positive effects of walking on treadmill with partial body weight support seems to be beneficial for children with Down syndrome [27] we did not find articles addressing it in CdLS. It is known that crawling has dissociated complex patterns of motion, requiring balancing the body in alternating movements, which may have been favored with gait training in suspension. It is also known that possibly the crawling acquisition influence on the gait acquisition [28]. In this case, as the gait is still not possible as an independent ability, the training of this activity in suspension may have influenced positively the gains of the less complex motor functions.

The higher quantitative gains observed in this case report in relation to patients with CP from other studies [29] may be due to the clinical nature of the pathology and its neuromotor changes. Although CdLS present several phenotypic changes [9] which influence directly in the motor development, this syndrome can present tone changes as hypertony found in the facial region of our patient, without changes in trunk and limbs. Thus, when we make a parallel with children with CP it is possible to note greater gains in those who had less impairments (GMFCS I and II; gains of 4.5%) [30] and less tone alteration.

An important detail of the INMT protocol is the existence of maintenance periods, in which the child continues to receive an intervention with a lower workload when compared with a module, in order to maintain motor skills acquired in the modules and promote a recovery. These maintenance periods for this case of CdLS show some drop in scores that could reflect the non-retention and/or learning of some skills, which could indicate the need for daily intervention with less workload or indicate cognitive aspects influencing the acquisition of motor skills assessed, since this syndrome affects this aspect. Longitudinal evaluation, even during periods without intervention, is suggested for a better understanding of the evolution of similar cases.

Other important information regarding INMT for children with CdLS refers to the transfer of motor functions gains from the physical therapy activities

for daily activities, reported by the child's mother. Transfers of intensive training for daily activities had also been reported in children with CP [30]. Thus, according to an ecological vision, the INMT improved the gross motor function of the patient with CdLS, when assessed by GMFM-88 and it facilitated his participation in some daily activities according to ICF domains (evaluated by parents).

One limitation of the study was the non-blinding of the evaluator.

Although INMT resulted in improvements in gross motor function and participation during daily activities in a child with CDLS, more studies are needed to bring scientific evidence of the effect of physical therapy (INMT) in children with CdLS, with a larger sample and comparison with other forms of intervention.

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