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Research Report

Can the CHOP-INTEND be used as An Outcome Measure in the First Months of Age? Implications for Clinical Trials and Real World Data

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Abstract.
Background: The CHOP-INTEND is an established outcome measure used to assess motor function in young and weak SMA patients previously validated in type I infants older than 3 months.
Objective: The aim of our study was to assess the maturation of the CHOP-INTEND scores in a group of healthy infants, establishing which items of the scale can be reliably used in individuals younger than 3 months.
Methods: This is a prospective observational study. The whole cohort was divided into 5 age groups. Each of the 16 CHOP-INTEND items was analyzed looking at the frequency distribution of the scores in each age subgroup. An item was considered developmentally appropriate when > 85% of the infants achieved a full score.
Results: our study includes 61 assessments collected < 2 weeks, 25 at 2–4 weeks, 20 at 5–8 weeks, 25 at 9–12 weeks and 20 at 13–17 weeks. Eight of the 16 items were developmentally appropriate already in the first week and another by the end of the first month. The remaining 7 items had more variable responses in the first three months and full scores were consistently achieved only after the third month.

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Conclusions: Our findings suggest that the CHOP-INTEND can be used before the age of 3 months, but the results should be interpreted with caution, considering which items are developmentally appropriate at the time of testing. This will also help to establish whether the changes observed following early treatments are a sign of efficacy or at least partly reflect maturational aspects.

Keywords: CHOP-INTEND, outcome measure, SMA, motor function, maturation, early treatment

INTRODUCTION

Spinal muscular atrophy (SMA) is a neuromuscular disorder affecting the anterior horn cells of the spinal cord and brainstem, caused by a defect in the survival motor neuron (SMN) 1 gene [1]. SMA has been historically subdivided into different types according to symptom onset and maximum motor function achieved, with type I being the most severe phenotype [2]. Classically patients with SMA type I are diagnosed by 6 months and never achieve independent sitting with survival generally less than 2 years [3].

The natural history of SMA I patients has dramatically changed over time, as a result of a more pro-active approach in the standard of care (e.g. non-invasive ventilation and enteral feedings) [4, 5] and more recently of the advent of disease modifying therapies [6–8].

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) [9] is a validated motor outcome measure developed to assess motor function in SMA I patients. The scale has been largely used in clinical trials [6–8] and real world setting [10–13] to follow the progression of motor changes in SMA I.

Following the availability of different therapeutic approaches, increasing attention has been devoted to better understand early functional changes and how the CHOP-INTEND scores may change in the first months. This need has been further supported by the advent of neonatal screening for SMA that, allowing earlier identification of SMA patients, has made it possible to start early treatment in the first weeks after birth.

One of the concerns with the use of the CHOP-INTEND in newborns is that the scale was originally developed on a group of 26 weak infants with SMA I or other neuromuscular diseases, with a mean age of 11.5 months [9]. A subsequent paper reporting the validation of the scale included 27 patients, with a mean age of 49 months, all above the age of 3 months [14]. Data on 9 infants examined at different ages are also reported in the report of the baseline of the Neuronext study [15]. While the scale can be used already in the first weeks, a few items, such as reaching for an object or those exploring axial tone are not entirely appropriate for newborns at the time some neurological and developmental aspects are not completely mature in typically developing infants and some primitive reflexes are still present [16, 17].

Until now, no systematic study has been performed to explore possible physiological changes in typically developing children and to establish which items can be reliably used in newborns and young infants.

The aim of our study was to assess and evaluate the distribution of the scores in the individual CHOP-INTEND scores in a cohort of typically developing newborns and infants, in order to establish which items can be reliably used in newborns and infants less than 3 months of age.

MATERIALS AND METHODS

This is a prospective, observational, cross-sectional study performed at the Fondazione Policlinico Gemelli (Rome) on healthy newborns and infants collected from June 2021 to October 2022. The study was approved by the ethics committee (Protocol n° 00006745/20) and written informed consent was obtained from all participants.

Participants were required to be born at term or near term without any indications of neurological impairment or suspected congenital or acquired abnormalities. Additionally, we excluded a history of reduced fetal movements, abnormalities in amniotic fluid, or ultrasound findings suggesting fetal anomalies or congenital infections. Infants with other perinatal or postnatal complications that could potentially impact neurological development (e.g., birth asphyxia, stroke, infectious disorders) were also excluded from the study.

Very early assessments were collected at the time of the routine pre-discharge neonatal examination (between 24 and 48 hours of age). Older newborns and infants were assessed during the routine pediatric follow-up visits. Preliminary data obtained in a small cohort of newborns infant showed very small variability and distribution of the variables of inter-

est within each age group. Based on these findings a minimum sample size of 20 infants per age group was recommended.

The study participants were categorized into five distinct age groups: less than two weeks, 2–4 weeks, 5–8 weeks, 9–12 weeks, and 13–17 weeks. In Italy, it is customary in clinical settings to perform regular assessments on newborns at monthly intervals during the initial months of their lives. These assessments play a crucial role in monitoring infants' overall well-being and developmental progress. Hence, we deemed it appropriate to utilize this monthly interval as a basis for grouping the participants according to their age.

Demographic, auxological and birth information (e.g. type of delivery, Apgar score, gestational age) were also collected at the moment of the visit. Mann-Whitney U Test was used to compare differences in score between male and female.

An arbitrary cut-off point of 85% was chosen as the 15th centile to define values outside the optimal/normal range as previously reported by our group [18].

CHOP-INTEND

The CHOP-INTEND is a valid and reliable tool, commonly used as an outcome measure in weak infants with type I SMA [9]. The tool includes 16 items and the total score ranges from 0 to 64, with higher scores indicating better motor abilities. Scoring for each item in based on a 4-point scale: no response (0), minimal (1), partial (2), nearly full (3) and complete (4) level of response.

CHOP-INTEND score sheet is reported in Supplementary material.

The CHOP-INTEND was performed and scored by two expert trained examiners, using standardised procedure of scale administration. The test was preferentially performed approximately 1 hour after feeding, on a firm padded mat, with babies wearing only nappy or body garment. The CHOP-INTEND was administered to infants in a behavioral status of 4 or 5 according to Brazelton behavioral assessment scale.

Each of the 16 CHOP-INTEND items were analyzed looking at the frequency distribution of the scores in each age subgroup. An item was considered developmentally appropriate when > 85% of the infants achieved a full score of 4. The CHOP-INTEND assessment in our study was conducted by two expert clinical evaluators, RDS and GC. Both evaluators have undergone extensive training in clinical trials through various programs [18], ensuring their expertise in performing the assessment. The inter-rater reliability showed a strong level of agreement with an coefficient exceeding 0.90. The range of differences in scores between the two raters fell within ± 1 point on the CHOP-INTEND assessment scale.

Test-retest reliability was assessed on five newborn infants, all aged less than two weeks, with a one-day interval between the assessments. Both examiners independently assessed the 5 infants using the CHOP-INTEND assessment on two consecutive days. The scores from the first were compared to the second evaluations using Pearson's correlation coefficient. The correlation coefficient exceeded 0.90, indicating a high level of agreement and consistency in the scores obtained from the two evaluations. The range of differences in scores between the initial and follow-up evaluations for test-retest reliability was within ± 2 points on the CHOP-INTEND assessment scale.

RESULTS

The attention was initially focused on the assessments performed in the neonatal period, collecting a total of 61 assessments during the routine pre-discharge neonatal examination (between 24 and 48 hours of age) or during the first week paediatric routine control. Another 25 newborns were examined between 2 and 4 weeks after birth. Another 20 infants were examined at 5–8 weeks, 25 at 9–12 weeks and 20 at 13–17 weeks. Of the 160 families asked to participate, only 15 refused (less than 10%). Only 3 infants were followed across two time points and one was followed at 4 time points, for a total number of 151 assessments obtained by a sample of 145 infants.

There was no bias in selection as, on the days when the examiners attended the neonatal unit or the follow up clinic, consent was obtained by the parents of all infants.

Demographic, auxological and birth information of the whole sample are summarized in Table 1.

On the CHOP-INTEND, eight of the 16 items had responses that were developmentally mature in over 85% of the infants already in the first week. These included spontaneous movement of upper extremities (item 1), spontaneous movement of lower extremities (item 2), hand grip (item 3), head in line with

Table 1
Characteristics of the whole sample

	Newborns ($n=86$)	Infants ($n=65$)
Gender, *n* (%)		
Females	44 (51%)	35 (54%)
Males	42 (49%)	30 (46%)
Delivery, *n* (%)		
Vaginal	61 (71%)	45 (69%)
Cesarean	25 (29%)	20 (31%)
Gestational Age (GA), *n* (%)		
35–36 weeks	7 (8%)	5 (8%)
≥37 weeks	79 (92%)	60 (92%)
Birth weight for GA, mean grams (SD)		
35–36 weeks	2498 (196)	2806 (604)
≥37 weeks	3289 (417)	3358 (427)
5′ Apgar for GA, mean points (SD)		
35–36 weeks	8.6 (0,5)	8,8 (0.5)
≥37 weeks	9.5 (0,5)	9.5 (0.5)
Ethnicity, *n* (%)		
Caucasian	80 (93%)	62 (95%)
Other	6 (7%)	3 (5%)
CHOP INTEND TOTAL SCORE, mean (SD)		
	All: 55 (3)	All: 60 (4)
	<2 w: 54 (3)	5–8 w: 58 (3)
	2–4 w: 56 (3)	9–12 w: 58 (3)
		13–17 w: 64 (2)

visual stimulation (item 4), hip adductors (item 5), hip flexion & foot dorsiflexion (item 11), elbow flexion (item13) and spinal incurvation (item 16).

One additional item (item 15) had responses that were developmentally mature by the end of the first month. The remaining 7 items had more variable responses in the first three months and had responses that were developmentally mature in over 85% of the infants after the third month (13–17 weeks). Frequency distribution of the full scores [4] on the CHOP-INTEND in each age subgroup are reported in Table 2.

No statistically significant difference was found between male and female performance on the scale (Mann-Whitney U Test for independent samples: $p=0.966$).

DISCUSSION

The CHOP-INTEND has been increasingly used in clinical and research settings as a tool to evaluate possible functional changes in relation to the new therapeutic options in SMA [6–8, 10–13] and in other neuromuscular disorders of infancy, e.g. myotubular myopathy. As no systematic reference data are available for infants younger than 3 months, we aimed to assess the early changes occurring in typically developing infants in order to establish which items of the scale can be reliably used in infants less than 3 months of age and provide a comparison for treated and untreated young SMA infants.

Our results showed that a full score is not consistently achieved on all the items of the scale before the age of 13 weeks. While a number of items can be easily administered obtaining full scores already in the first weeks after birth as they are developmentally appropriate, other aspects of function assessed by other items are not consistently mature. Because of

Table 2
The week interval in which the optimality score was achieved by each age subgroups

	<2 weeks *N=61*	2–4 weeks *N=25*	5–8 weeks *N=20*	9–12 weeks *N=25*	13–17 weeks *N=20*
Item 1	100%	100%	100%	100%	100%
Item 2	100%	100%	100%	100%	100%
Item 3	98%	100%	90%	100%	100%
Item 4	90%	88%	100%	96%	100%
Item 5	98%	100%	100%	100%	100%
Item 6*	8%	16%	50%	48%	95%
Item 7*	7%	12%	45%	44%	95%
Item 8*	54%	76%	65%	68%	95%
Item 9*	38%	48%	30%	44%	95%
Item 10**	11%	28%	60%	24%	100%
Item 11	100%	100%	100%	100%	100%
Item 12**	3%	4%	5%	4%	95%
Item 13	87%	85%	90%	92%	100%
Item 14**	54%	56%	75%	72%	100%
Item 15**	75%	92%	95%	100%	100%
Item 16	97%	100%	95%	100%	100%

*The range of scores for items 6, 7, 8 and 9 was between 2 and 4; **the range of scores for items 10, 12, 14 and 15 was between 0 and 4.

this, none of the typically developing newborns had a full total score of 64. A full total score was achieved at 8 weeks but only in a few infants with an increasing number of infants reaching a full score between 8 and 12 weeks. Full total scores were consistently observed only after the age of 13 weeks. We identified no sex differences in the distribution of results. One limitation of this study is the limited ethnic and racial diversity of our population as 94% were of Caucasian origin.

The items that were developmentally appropriate already in the first weeks, showing full scores in over 85% of newborns at that age, were related to spontaneous or elicited movement of upper and lower extremities and head control in the supine position. Not surprisingly, the items that were not equally mature were those requiring a more mature axial tone with head and trunk control.

The maturation of some functional changes on the CHOP-INTEND is in line with the findings from structured infant neurological examinations, such as the Hammersmith Infant neurological examination [16, 17] or the Touwen examination [19], showing that axial tone, head control and movements are not fully mature until the age of approximately 3 to 4 months.

The increase in scores within the first 4 months of life is not linear, with a substantial jump between 9–12 and 13–17 weeks (roughly between 3 and 4 months), likely reflecting developmental maturation of axial tone and strength.

The changes in scores in the first 3 months should not be a reason for not using the CHOP-INTEND before that age. Despite the limitations of the relatively small numbers in each subgroup, our results suggest that before the age of 3 months the CHOP-INTEND can be used but the results should be interpreted with caution. Before that age, not achieving a full score on some items should not be considered as an abnormal finding.

We suggest that the items that are known to be not consistently mature could be identified in the CHOP-INTEND form so that, when using the scale in younger infants, the examiner is aware of the items that are developmentally appropriate at different ages. The scale could therefore be scored using the full scales or, if aimed at establishing how many items are suboptimal for age, only including, in the interpretation of the results, those items that are expected to be achieved by 85% of infants that age. For example, infants evaluated in first days of life would have the full CHOP-INTEND administered and a total score obtained, but in the interpretation only include 8 of the 16 items with a maximum normative score of 32. Likewise, between 2 and 12 weeks of age the maximum normative score would be 36 points, with a jump to a full 64 points after 13 weeks.

These findings will also help in the interpretation of the changes observed in treated SMA infants. Until now, an improvement of the CHOP-INTEND scores in patients treated in the neonatal period were often interpreted as a sign of efficacy while, they were possibly partly reflecting maturational aspects.

A better understanding of the maturational changes of the CHOP-INTEND is also relevant at the time when infants with *SMN* mutations are identified through neonatal screening. Recent papers suggest that some of these infants may not be completely asymptomatic and be in a prodromic stage [20] with possible minor neurological signs [21]. It will be interesting to establish whether infants identified through screening with 2 *SMN2* copies or with minimal neurological signs, when treated in the first weeks, will diverge from the pattern of maturation observed in our cohort of typically developing infants.

CONFLICT OF INTEREST

Costanza Cutrona, Anna Capasso, Martina Ricci, Giulia Stanca, Sara Carnicella, Meric Utlulig Rita Luciano, Gianni Vento, Giulia Bersani and Ilaria Lazzareschi have no conflict of interest to report.

Roberto de Sanctis reports personal fees from Biogen S.R.L. Italia, AveXis, and Novartis outside the submitted work;

Giorgia Coratti reports personal fees from Biogen S.R.L. Italia, Roche, Genesis Pharma, AveXis, Novartis, and Biologix, outside the submitted work;

Danilo Buonsenso reports personal fees from Qiagen and Pfizer and participation at advisory board for Pfizer outside the submitted work;

Richard S. Finkel is Pi and part of advisory boards for AveXis, Novartis, Roche, Biogen S.R.L., Scholar Rock, Cytogenetics outside the submitted work.

Marika Pane reports personal fees from Biogen S.R.L., PTC, AveXis, Novartis, and Sarepta, outside the submitted work;

Eugenio Mercuri is Pi and part of advisory boards for AveXis, Novartis, Roche, Biogen S.R.L., Scholar Rock, Epirium outside the submitted work.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JND-221644.

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