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Serum nerve growth factor and early motor neuropathy in children receiving neurotoxic chemotherapy: a prospective single-center cohort study

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Abstract

Purpose

No circulating biomarker identifies children at risk of chemotherapy-induced peripheral neuropathy before symptoms appear. We examined whether serum nerve growth factor (NGF) predicts incident motor neuropathy.

Methods

Twenty-eight children starting vincristine, cisplatin or carboplatin at one tertiary pediatric center were enrolled prospectively. Serum NGF was measured by ELISA before the course and on days 7 and 30, with standardized neurological examination at each point. Groups were compared by Mann–Whitney U test, within-patient change by Friedman and Wilcoxon tests, the group-by-time interaction by mixed-effects modelling, and discrimination by ROC analysis.

Results

Median age was 4.6 years (range 2.0–16.9); 24 children (85.7%) received vincristine. Motor neuropathy developed in 8 children (28.6%, 95% CI 15.3–47.1; 33.3% of vincristine recipients), resolving in seven of eight. Serum NGF did not differ between groups at any time point ($p = 0.218–0.611$) and did not discriminate neuropathy (all AUC ≤ 0.66). NGF rose significantly across the month in children without neuropathy (Friedman $p = 0.024$) but not in those with neuropathy ($p = 0.417$); the group-by-time interaction was not significant ($p = 0.160$). Lower cumulative vincristine dose in affected children ($p = 0.040$) depended on a single outlier and did not survive correction for multiplicity.

Conclusion

Serum NGF did not predict motor neuropathy and cannot be recommended as a biomarker; the trajectory divergence is hypothesis-generating only. One in three vincristine-treated children developed motor neuropathy detectable by bedside examination within a month of a single course, supporting systematic neurological assessment from the outset of vinca alkaloid therapy.

Introduction

Survival after childhood cancer now exceeds 80% in high-income settings, and treatment-related morbidity has become correspondingly central to pediatric oncology practice [1, 2]. Chemotherapy-induced peripheral neuropathy (CIPN) is among the most common dose-limiting toxicities in this population. It may present with sensory, motor or autonomic features, commonly as pain, paresthesia,

weakness or difficulty walking, and can persist after treatment ends, affecting school participation, physical function and quality of life [3, 4].

Vincristine, used in most pediatric leukemia, lymphoma and solid tumor protocols, is the principal cause of CIPN in children. By disrupting microtubule dynamics it impairs axonal transport, producing a length-dependent axonal neuropathy with prominent motor involvement, a pattern that distinguishes pediatric vincristine neuropathy from the predominantly sensory syndromes seen with platinum agents and taxanes in adults [5]. Reported incidences range from 19% to 85%, a spread driven largely by differences in assessment method, follow-up duration and case definition [4, 6]. Susceptibility is markedly heterogeneous. Cumulative dose is intuitively appealing as a risk factor, yet several studies have found no relationship between cumulative vincristine exposure and long-term motor outcome [7], and the best-validated determinant identified to date is genetic, namely homozygosity for the T allele at CEP72 rs924607 [8].

This heterogeneity matters clinically because no agent has been shown to prevent CIPN; dose modification and early recognition remain the only available levers [9]. Validated pediatric assessment instruments exist, notably the pediatric-modified Total Neuropathy Score (ped-mTNS), but they require an examination that young or unwell children may not tolerate, and they detect neuropathy only once it has developed [10]. A circulating biomarker identifying vulnerable children before clinical onset would fill a genuine gap in supportive care, allowing surveillance and dose modification to be targeted at those most likely to benefit.

Nerve growth factor (NGF) is the prototypical neurotrophin and is essential to the development, survival and repair of sympathetic and small-fibre sensory neurons, with additional trophic effects on motor units. Because neurotrophin availability plausibly determines how well an axon withstands and recovers from microtubule injury, NGF is a biologically coherent candidate. In adults, reduced circulating NGF has been associated with emerging neurotoxicity during platinum- and taxane-based regimens [11], and NGF depletion has been reported in adults with hematological malignancies who develop CIPN [12]. Whether these observations extend to children, in whom neural plasticity, growth and neurotrophin turnover differ substantially, is unknown.

We therefore conducted an exploratory prospective cohort study to determine whether serum NGF, measured before a course of neurotoxic chemotherapy and again at 7 and 30 days, is associated with incident motor neuropathy in children, and whether baseline NGF or its early trajectory discriminates those who develop clinically detectable CIPN.

Methods

Study design and participants

This prospective, single-center observational cohort study was conducted in the Division of Pediatric Hematology and Oncology, Sakarya Training and Research Hospital, Türkiye, between October 2021 and

October 2022, and is reported in accordance with the STROBE recommendations [13]. Consecutive patients admitted for a course of chemotherapy containing a neurotoxic agent (vincristine, cisplatin or carboplatin) were screened. Eligibility required a neurotoxic agent in the protocol, a normal pre-treatment serum vitamin B12 concentration, and informed consent. Children with a neurological disorder antedating the cancer diagnosis and those declining participation were excluded. Twenty-eight children were enrolled; none was lost to follow-up and no measurement was missing.

Serum NGF measurement

Venous blood was drawn into plain tubes on day 0 (the day before the chemotherapy course), day 7 and day 30. Samples were centrifuged within 15 min and the separated serum stored at −80 °C until batched analysis. NGF was quantified by sandwich ELISA (Human NGF ELISA, Elabscience, Cat. No. E-EL-H1205; sensitivity 18.75 pg/mL) on a BIO-TEK ELx800 microplate reader with an ELx50 strip washer. All samples were assayed in a single batch to avoid inter-assay drift, and laboratory personnel were unaware of the clinical findings.

Neurological assessment and outcome definition

A standardized bedside neurological examination was performed on days 0, 7 and 30 by the treating pediatric team, comprising deep tendon reflexes (normoactive or hypoactive), segmental muscle strength on the 0–5 Medical Research Council scale, and observation of gait. Sensory examination was attempted in children able to cooperate, and autonomic symptoms were elicited by structured parental interview. The outcome was incident motor neuropathy by day 30, defined as a priori as newly hypoactive deep tendon reflexes together with demonstrable muscle weakness in a child with a normal day-0 examination. Nerve conduction studies were obtained in a subset for clinical indications but were not protocolized and are not reported. A final examination documented resolution. The cumulative dose of each neurotoxic agent administered up to the final study assessment was extracted from the treatment record.

Statistical analysis

Analyses were performed in IBM SPSS Statistics 25.0. Continuous variables are summarized as mean ± standard deviation and median with 25th–75th percentiles and range; categorical variables as counts and percentages. Distributions departed from normality, so between-group comparisons used the Mann–Whitney U test with the rank-biserial correlation as effect size; proportions were compared by Fisher's exact test or the Fisher–Freeman–Halton test, and the incidence of neuropathy is reported with a Wilson 95% confidence interval.

Within-patient change across the three sampling points was tested by the Friedman test with Wilcoxon signed-rank post hoc comparisons, performed separately in each group. Because a difference in within-group significance is not equivalent to a significant between-group difference, the group-by-time interaction was tested directly in a linear mixed-effects model of serum NGF with fixed effects for sampling point, group and their interaction and a random intercept for each child, using a two-degree-of-freedom Wald test. Discrimination was assessed by receiver operating characteristic (ROC) analysis, with areas under the curve (AUC) reported with Hanley–McNeil standard errors and 95% confidence intervals, and by univariable logistic regression with odds ratios per 100 pg/mL. Two-sided $p < 0.05$ denoted nominal significance. Because the analysis was exploratory and multiple comparisons were performed, Holm-adjusted and Benjamini–Hochberg false-discovery-rate-adjusted p values are additionally reported for the primary set of eight group comparisons.

No a priori sample-size calculation was performed; the sample comprised all eligible children admitted during the 12-month recruitment window. Post hoc, a comparison of 20 against 8 participants has approximately 80% power at $\alpha = 0.05$ to detect only a very large, standardized difference of about 1.2 standard deviations, whereas the largest observed between-group effect was 0.69 standard deviations. The study was therefore adequately powered to exclude large effects alone, and null findings should be read as inconclusive rather than as evidence of no association.

Ethics

The protocol was approved by the Clinical Research Ethics Committee of Sakarya University Faculty of Medicine (approval no. 70464-174, 14 October 2021) and the study was performed in line with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants, with assent from older children where appropriate.

Results

Cohort characteristics and incidence of neuropathy

Twenty-eight children were enrolled: 17 boys (60.7%) and 11 girls (39.3%). Mean age was 6.6 ± 4.6 years, median 4.6 years (IQR 3.4–8.8; range 2.0–16.9). Leukemia was the commonest diagnosis (17 children, 60.7%), followed by lymphoma (4, 14.3%). Twenty-four children (85.7%) received vincristine, three (10.7%) cisplatin and two (7.1%) carboplatin; one child treated for Ewing sarcoma received both vincristine and carboplatin. Baseline characteristics are shown in Table 1.

Motor neuropathy developed in 8 of 28 children (28.6%, 95% CI 15.3–47.1). All eight had received vincristine, an incidence of 33.3% (95% CI 18.0–53.3) among the 24 vincristine recipients; no child treated only with a platinum agent was affected. Every affected child had both hypoactive deep tendon reflexes and difficulty walking; muscle strength was graded 2/5 in three children, 3/5 in four and 4/5 in one. Findings had resolved by the final assessment in seven of eight children; the eighth died of sepsis,

unrelated to neuropathy. Affected children were younger than unaffected children (4.3 ± 1.4 vs 7.5 ± 5.1 years) but the difference was not significant (p = 0.321). All eight cases occurred among children with leukemia (5 of 17) or lymphoma (3 of 4) and none among the seven children with other diagnoses, so the distribution of diagnoses differed between groups (Fisher–Freeman–Halton p = 0.035); the excess among lymphoma patients considered alone did not reach significance (p = 0.058) and, resting on four children in total, should not be over-read. Sensory examination was interpretable in only a minority of children given the young median age of the cohort, and no autonomic syndrome was identified by parental report, so the analysis rests on the motor endpoint.

Serum NGF and motor neuropathy

For the cohort, serum NGF was 312.2 ± 195.6 pg/mL at day 0 (median 319.2; range 16.7–727.7), 393.8 ± 165.4 pg/mL at day 7 and 408.8 ± 203.8 pg/mL at day 30, a significant rise overall (Friedman $\chi^2 = 8.00$, p = 0.018). Serum NGF did not differ significantly between children who developed motor neuropathy and those who did not at any time point (Table 2). Children who went on to develop neuropathy had numerically higher concentrations at day 0 and day 7 but lower concentrations at day 30, so that the two trajectories crossed between days 7 and 30 (Fig. 1).

Longitudinal analysis makes the pattern clearer. Among children who remained neurologically intact, serum NGF rose significantly across the month (Friedman $\chi^2 = 7.50$, p = 0.024; day 0 vs day 30 p = 0.006), whereas among children who developed motor neuropathy no significant change occurred at any interval (Friedman $\chi^2 = 1.75$, p = 0.417; all pairwise p ≥ 0.383). In the mixed-effects model, NGF in the unaffected group increased by 93.0 pg/mL at day 7 (95% CI 15.0–171.0, p = 0.019) and by 136.2 pg/mL at day 30 (95% CI 58.2–214.2, p = 0.001) relative to baseline; the corresponding interaction terms for the neuropathy group were −39.8 pg/mL (p = 0.593) and −138.5 pg/mL (p = 0.063), and the overall group-by-time interaction was not significant (Wald $\chi^2 = 3.67$, 2 df, p = 0.160). Consistent with this, the between-group comparison of within-patient change scores was non-significant at every interval (p = 0.182–0.199; Fig. 2), with a Cohen's d of −0.69 for the day 30 minus day 0 contrast. Restricting the analysis to the 24 vincristine recipients gave the same pattern, the day 30 minus day 7 contrast being closest to conventional significance (69.6 ± 178.3 vs −55.5 ± 162.0 pg/mL, p = 0.093).

Discriminative performance and cumulative dose

No NGF measure discriminated against children who developed motor neuropathy (Table 3). The highest area under the curve was 0.656 for NGF at day 7 (95% CI 0.420–0.893, p = 0.195); baseline NGF gave 0.628 (95% CI 0.389–0.868, p = 0.294). Every confidence interval included 0.5, and change scores performed no better (AUC 0.331–0.338). In univariable logistic regression no NGF value or change score was associated with the outcome, the strongest estimate being an odds ratio of 0.70 per 100 pg/mL for the day 30 minus day 0 change (95% CI 0.44–1.10, p = 0.121).

Children who developed motor neuropathy had received a lower cumulative vincristine dose than those who did not (4.9 ± 1.7 vs 8.6 ± 10.5 mg/m², p = 0.040). The group medians were identical at 6.0 mg/m², and the difference arose entirely from a single child with Wilms tumor whose protocol delivered 48 mg/m²; excluding that observation the comparison became non-significant (p = 0.055). Across the eight primary group comparisons this was the only nominally significant result, and it did not survive adjustment for multiplicity (Holm-adjusted p = 0.320; Benjamini–Hochberg p = 0.320).

Discussion

In this prospective cohort of 28 children receiving neurotoxic chemotherapy, serum NGF measured before treatment and at 7 and 30 days did not distinguish children who developed motor neuropathy from those who did not. Neither absolute concentrations nor within-patient change scores showed useful discrimination, with every area under the curve below 0.66 and every confidence interval crossing 0.5. On these data, serum NGF cannot be recommended as a stand-alone predictive biomarker for CIPN in children.

The longitudinal analysis is the most interesting result. Serum NGF rose significantly across the month in children who remained neurologically intact, an increase of 136 pg/mL by day 30, while in children who developed motor neuropathy concentrations did not change significantly at any interval. One reading is that a sustained rise in circulating neurotrophin represents a compensatory trophic response to subclinical axonal injury, and that failure to mount or maintain that response accompanies clinically manifest neuropathy. This would be consistent with the NGF depletion reported in adults with hematological malignancies who develop CIPN [12] and with the association between circulating NGF and neurotoxicity during platinum- and taxane-based treatment in adults [11].

That interpretation must be advanced with caution, for a reason that is easy to overlook. The difference in within-group significance is not the same as a significant difference between groups. When the interaction was tested directly it did not reach significance (p = 0.160), and the between-group comparison of change scores was likewise non-significant at every interval. The divergence may simply reflect the much smaller neuropathy group, in which an increase of comparable magnitude would not have achieved significance. The day-30 interaction term (− 138.5 pg/mL, p = 0.063) and the moderate effect size (d = − 0.69) indicate a signal worth pursuing in an adequately powered study, but on present evidence the trajectory divergence is a hypothesis, not a finding.

The apparent inverse relationship between cumulative vincristine dose and neuropathy warrants interpretation rather than the counter-intuitive causal reading invites. Cumulative dose is not a fixed baseline attribute but a quantity that accrues with time on treatment, and here it was measured at the point of final assessment. Children who developed neuropathy did so early, and their exposure was counted at that early point; children who remained unaffected continued therapy and accumulated more drug before their exposure was tallied. Analyzing a time-varying exposure as though it were a baseline covariate induces a spurious inverse association, a variant of immortal-time bias. Our data support this

reading directly: median doses were identical, the difference in means was generated by a single child on a Wilms tumor protocol, removing whom abolished significance, and the result did not survive correction for multiplicity. The data are therefore consistent with vincristine neurotoxicity emerging early, at modest cumulative exposure, in a susceptible subset of children, not with higher doses being protective. This aligns with electrophysiological work describing atypical, early patterns of vincristine neuropathy in children [14], with the absence of any relationship between cumulative dose and long-term motor performance [7], and with the substantial contribution of host genotype to individual susceptibility [8].

The incidence we observed is clinically salient. One in three vincristine-treated children showed unequivocal motor signs within thirty days of a single course, detected by nothing more elaborate than a careful bedside examination. This lies within the wide published range for pediatric CIPN [4, 6] and reinforces the case for systematic neurological assessment from the very start of vincristine-containing therapy rather than at the point of symptomatic complaint, a low-cost change in supportive care practice that requires no new technology. That findings resolved in seven of eight children is reassuring, but resolution over one month does not exclude persistent subclinical deficits, which longer follow-up with validated instruments would be needed to detect.

Several limitations constrain what can be concluded. The cohort is small and single-center, and only very large effects could have been detected; the null results are inconclusive rather than negative. Neuropathy was ascertained by routine clinical examination rather than by a validated pediatric instrument such as the ped-mTNS [10] or by formal CTCAE grading, which almost certainly underestimates mild and sensory disease and limits comparability with other cohorts. The median age of 4.6 years meant that sensory testing was uninterpretable in most children and autonomic assessment relied on parental reports. Nerve conduction studies were performed only for clinical indications and were not analyzed. The cohort was diagnostically heterogeneous and treated on several protocols, with concomitant neurotoxic and supportive medications unaccounted for. There was no healthy control group and no pediatric reference interval for serum NGF, so absolute concentrations cannot be interpreted against any external standard. Serum rather than plasma was assayed; circulating neurotrophin concentrations are influenced by platelet content and release during clotting, a consideration of weight in a population with frequent chemotherapy-induced thrombocytopenia, and platelet counts were not incorporated. Follow-up extended only to 30 days after a single course, so chronic and cumulative CIPN were not captured. Finally, multiple comparisons were performed, and the single nominally significant result did not survive adjustment.

Against these limitations, the study has real strengths. Prospective serial sampling at three predefined time points with complete follow-up and no missing measurements, concurrent clinical phenotyping, and a longitudinal analysis that tests the group-by-time interaction directly rather than relying on within-group comparisons are uncommon in pediatric CIPN research, and data on neurotrophin biology in children receiving neurotoxic chemotherapy remain scarce. Future work should couple a validated CIPN instrument and standardized nerve conduction studies with multi-center recruitment, incorporate CEP72 and other candidate pharmacogenetic variants, and evaluate NGF alongside other neurotrophins and

axonal injury markers, neurofilament light chain in particular, within a panel rather than as a single analyte.

Conclusion

Serum NGF did not predict motor chemotherapy-induced peripheral neuropathy in children, whether measured at baseline or as an early trajectory, and cannot be recommended as a stand-alone biomarker on present evidence. Serum NGF rose significantly during the first month of neurotoxic chemotherapy in children who remained neurologically intact but not in those who developed neuropathy; because the group-by-time interaction was not significant, this divergence remains a hypothesis for adequately powered study. The inverse association with cumulative vincristine dose is most plausibly an artefact of time-dependent exposure and outlier influence. For supportive care practice, the actionable message is that motor neuropathy appeared in a third of vincristine-treated children within a month of a single course and was detectable by routine bedside examination, which argues for systematic neurological assessment from the beginning of treatment in every child receiving vinca alkaloids.

Abbreviations

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Declarations

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Author contributions Conceptualization: İrem Türkoğlu Kuzu, Mehmet Fatih Orhan; Methodology: Mehmet Fatih Orhan; Formal analysis and investigation: İrem Türkoğlu Kuzu, Mehmet Fatih Orhan; Writing – original draft preparation: İrem Türkoğlu Kuzu; Writing – review and editing: Mehmet Fatih Orhan; Funding acquisition: Mehmet Fatih Orhan; Supervision: Mehmet Fatih Orhan. Both authors read and approved the final manuscript.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Clinical Research Ethics Committee of Sakarya University Faculty of

Medicine (14 October 2021 / No. 70464-174).

Consent to participate Written informed consent was obtained from the parents or legal guardians of all children included in the study, with assent from older children where appropriate.

Consent to publish Not applicable; the manuscript contains no individually identifiable data, images or videos.

Data availability The de-identified dataset generated and analyzed during the current study is not publicly available because the consent obtained from participants' guardians did not cover public deposition but is available from the corresponding author on reasonable request.

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Tables

Table 1 Baseline characteristics of the cohort (n = 28)

Characteristic	Total (n = 28)	No neuropathy (n = 20)	Motor neuropathy (n = 8)	p
Sex				**0.671**
Male	17 (60.7)	13 (65.0)	4 (50.0)	
Female	11 (39.3)	7 (35.0)	4 (50.0)	
Age, years				**0.321**
Mean ± SD	6.6 ± 4.6	7.5 ± 5.1	4.3 ± 1.4	
Median (IQR)	4.6 (3.4–8.8)	5.8 (3.4–12.3)	4.2 (3.5–5.3)	
Range	2.0–16.9	2.0–16.9	2.0–6.2	
Diagnosis				**0.035**
Leukemia	17 (60.7)	12 (60.0)	5 (62.5)	
Lymphoma	4 (14.3)	1 (5.0)	3 (37.5)	
Germ cell tumor	2 (7.1)	2 (10.0)	0	
Malignant bone tumor	2 (7.1)	2 (10.0)	0	
Nasopharyngeal carcinoma	1 (3.6)	1 (5.0)	0	
CNS tumor	1 (3.6)	1 (5.0)	0	
Wilms tumor	1 (3.6)	1 (5.0)	0	
Neurotoxic agent				**0.295**
Vincristine	24 (85.7)	16 (80.0)	8 (100)	
Cisplatin	3 (10.7)	3 (15.0)	0	
Carboplatin	2 (7.1)	2 (10.0)	0	
Cumulative dose, mg/m², median (range)				
Vincristine	6.0 (1.5–48.0)	6.0 (4.5–48.0)	6.0 (1.5–6.0)	0.040
Cisplatin	160 (120–200)	160 (120–200)	—	—
Carboplatin	1,150 (1,100–1,200)	1,150 (1,100–1,200)	—	—

Values are n (%) unless stated otherwise. Sex and neurotoxic agent were compared by Fisher's exact test, age and cumulative vincristine dose by the Mann–Whitney U test, and diagnosis by the Fisher–Freeman–Halton exact test on the three-level grouping leukemia / lymphoma / other. One child with Ewing sarcoma received both vincristine and carboplatin, so agent counts exceed the cohort total; a

second child, treated for a yolk sac tumor, was recorded as receiving vincristine in the dose field and was classified accordingly. Doses are those administered up to the final study assessment. CNS central nervous system, IQR interquartile range, SD standard deviation

Table 2 Serum nerve growth factor by neuropathy status

	No neuropathy (n = 20) mean ± SD	No neuropathy median (IQR)	Motor neuropathy (n = 8) mean ± SD	Motor neuropathy median (IQR)	p
Concentration, pg/mL					
Day 0	280.9 ± 187.4	307.5 (91.2–417.8)	390.6 ± 205.8	351.4 (286.5–536.4)	0.309
Day 7	373.8 ± 157.2	354.3 (274.9–510.3)	443.8 ± 185.5	500.2 (376.6–564.0)	0.218
Day 30	417.1 ± 226.3	470.1 (200.2–586.8)	388.3 ± 143.4	354.1 (284.9–502.1)	0.611
Within-patient change, pg/mL					
Day 7 − day 0	93.0 ± 161.4	119.0 (21.8–163.8)	53.2 ± 134.4	9.1 (−3.4–84.1)	0.182
Day 30 − day 0	136.2 ± 188.8	87.0 (−9.6–304.6)	−2.4 ± 230.8	11.3 (−170.7–162.1)	0.199
Day 30 − day 7	43.2 ± 179.9	59.9 (−112.6–188.6)	−55.5 ± 162.0	−11.2 (−227.6–43.3)	0.199
Within-group change over time					
Friedman test	$\chi^2 = 7.50$	p = 0.024	$\chi^2 = 1.75$	p = 0.417	—
Wilcoxon, day 0 vs day 7	W = 39.0	p = 0.012	W = 11.0	p = 0.383	—
Wilcoxon, day 0 vs day 30	W = 34.0	p = 0.006	W = 17.0	p = 0.945	—
Wilcoxon, day 7 vs day 30	W = 78.0	p = 0.330	W = 12.0	p = 0.461	—

Between-group comparisons by the Mann–Whitney U test; within-group change across the three sampling points by the Friedman test with Wilcoxon signed-rank post hoc comparisons. None of the between-group p values remained significant after Holm or Benjamini–Hochberg adjustment across the eight primary comparisons (all adjusted p = 1.00). The group-by-time interaction tested in a linear mixed-

effects model was not significant (Wald $\chi^2 = 3.67$, 2 df, $p = 0.160$). IQR interquartile range, SD standard deviation

Table 3 Discriminative performance of serum nerve growth factor for incident motor neuropathy

Variable	AUC	SE	95% CI	p (ROC)	OR per 100 pg/mL (95% CI); p
NGF day 0	0.628	0.122	0.389–0.868	0.294	1.36 (0.86–2.16); 0.186
NGF day 7	0.656	0.121	0.420–0.893	0.195	1.33 (0.76–2.33); 0.312
NGF day 30	0.434	0.119	0.200–0.668	0.583	0.93 (0.62–1.40); 0.732
NGF change, day 7 − day 0	0.331	0.109	0.118–0.544	0.121	0.83 (0.47–1.48); 0.529
NGF change, day 30 − day 0	0.337	0.110	0.123–0.552	0.138	0.70 (0.44–1.10); 0.121
NGF change, day 30 − day 7	0.338	0.110	0.123–0.552	0.138	0.71 (0.42–1.19); 0.188
Age	0.375	0.114	0.152–0.598	0.273	0.79 (0.58–1.07) per year; 0.131

Standard errors and confidence intervals for the AUC by the Hanley–McNeil method; odds ratios from univariable logistic regression. Receiver operating characteristic curves are shown in Online Resource 1. AUC area under the receiver operating characteristic curve, CI confidence interval, NGF nerve growth factor, OR odds ratio, SE standard error

Figures

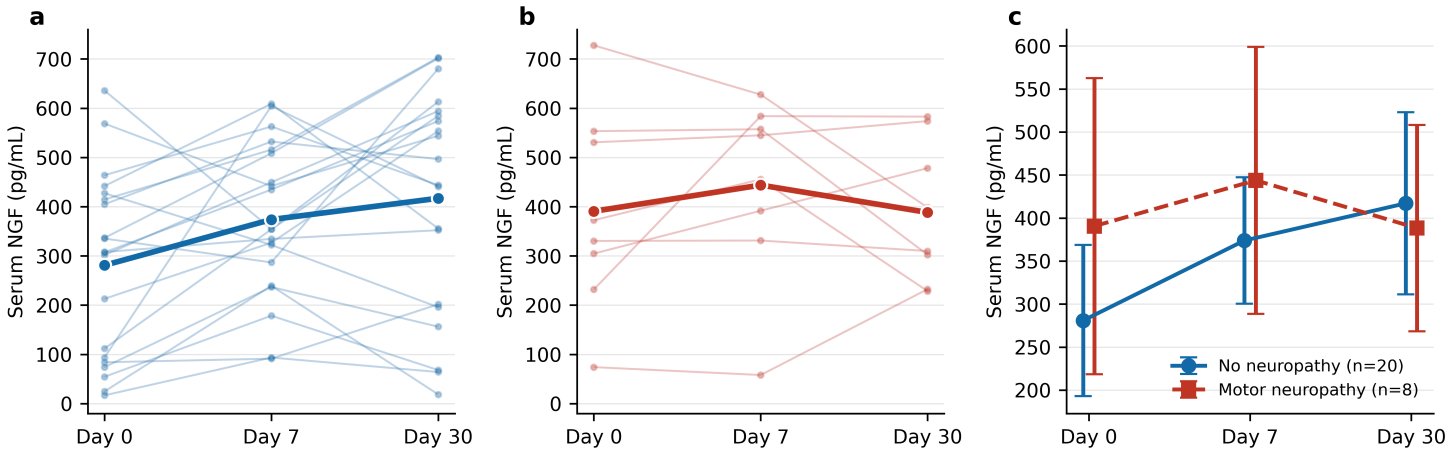


Figure 1

Serum nerve growth factor across the three sampling points.

a. Individual trajectories of the 20 children who did not develop motor neuropathy, with the group mean in bold.

b. Individual trajectories of the 8 children who developed motor neuropathy, with the group mean in bold.

c. Group means with 95% confidence intervals. Concentrations rose significantly in children who remained neurologically intact (Friedman p = 0.024) but did not change significantly in those who developed motor neuropathy (Friedman p = 0.417); the group-by-time interaction was not significant (p = 0.160)

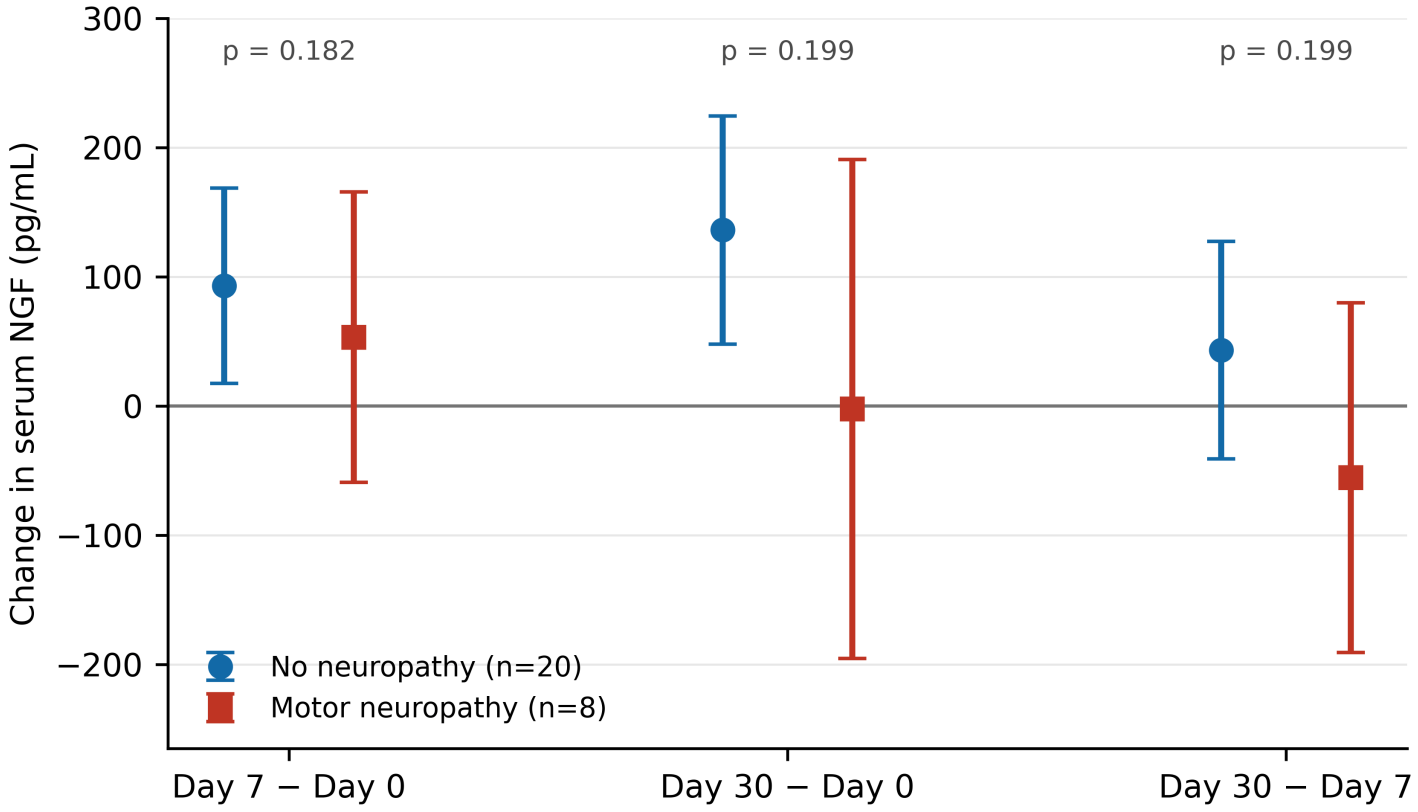


Figure 2

Within-patient change in serum nerve growth factor by neuropathy status, shown as group mean with 95% confidence interval. Confidence intervals for children who developed motor neuropathy include zero at every contrast, and no between-group comparison reached significance (Mann–Whitney U test)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ESM1.pdf