

Supplementary Online Content

Kandula T, Farrar MA, Cohn RJ, et al. Chemotherapy-induced peripheral neuropathy in long-term survivors of childhood cancer: clinical, neurophysiological, functional, and patient-reported outcomes. *JAMA Neurol*. Published online May 14, 2018. doi:10.1001/jamaneurol.2018.0963

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Description of clinical, neurophysiological, functional, and patient-reported outcome measures

Clinical and neurophysiological studies were administered by a single operator (TK) and standardised training was undertaken with each investigator administering the functional studies (TK, SP, KC, DM) to ensure consistent testing protocols. The type of testing protocol administered depended on the age of the participants. Children and adolescents were defined as <17 years and adults were ≥ 17 years of age.

Clinical measures

The clinical assessment was conducted using the total neuropathy score, clinical version (TNSc) in adults¹ or the modified-pediatric total neuropathy score (ped-mTNS) in children and adolescents.² The total neuropathy score is a clinical grading scale incorporating motor, sensory and autonomic symptom report as well as clinical examination of distal power and multiple sensory modalities (light touch, pin prick, vibration, deep tendon reflexes). Each modality is given a score out of four leading to a total score out of 28 for the TNSc and 32 for the ped-mTNS. In individual participants, a TNS of 0-1 is considered normal.³ The reliability and validity of both versions of the TNS has been demonstrated in the context of CIPN.^{2,4-6} The predominant difference between the adult and paediatric versions of the TNS score is the inclusion of light touch sensation in the ped-mTNS. This component was excluded from analysis allowing comparison across the adult and paediatric age groups.

Neurophysiological measures

Sensory and motor nerve conduction studies were performed utilising conventional techniques⁷ using the Medelec Synergy system (Oxford Instruments, Oxfordshire, UK) and included the antidromic sural sensory nerve, tibial motor nerve, deep peroneal motor nerve and median motor and sensory nerves. These were compared to the control group as well as age appropriate reference ranges.⁸⁻¹⁰

Functional measures

The Movement Assessment Battery for Children, 2nd edition (MABC) was administered to children and adolescents. While there are no specific paediatric functional measures available for testing peripheral neuropathy, the MABC is a global test of fundamental movement skills which includes measures that assess peripheral nerve function, and has been utilized in other studies assessing CIPN.¹¹⁻¹³ The MABC comprises of measures of manual dexterity (3 test items), aiming and catching (2 items) and balance (3 items), which are standardized for different age groups. Normative reference data is available for each age group.¹⁴ Scores were assigned for each test item and a composite score for each domain as well as a global functional score was calculated.

Individual tests of peripheral nerve function assessing manual dexterity and distal upper limb quantitative sensory tests were administered in adult participants. Von Frey monofilaments were used to test distal fingertip sensation in the index finger using graduated calibrated fine filaments.¹⁵ The grating orientation task, also administered in the index finger tested cutaneous spatial resolution using plastic domes with rectangular grooves of varying sizes.¹⁶ The grooved peg board tested manual dexterity and involved timed insertion of grooved pegs into slots.^{17,18}

Patient Reported Outcomes

The European Organisation for Research and Treatment of Cancer (EORTC) quality of life (QOL) questionnaire (QLQ-C30) Version 3 and the associated chemotherapy induced peripheral neuropathy questionnaire (CIPN20) were used to evaluate patient reported outcomes (PRO) in participants ≥ 17 years.⁶ The QLQ-C30 was subdivided into four key domains for analysis – physical and role functioning, psychosocial functioning, general symptom scale and global health status/QOL. The CIPN20 was considered as a total score as well as divided into the sensory, motor and autonomic subscales.

In the absence of paediatric CIPN specific PRO measures, the Paediatric Outcomes Data Collection Instrument (PODCI) developed for evaluation of physical disability in children with musculoskeletal disorders^{19,20} as well as the Paediatric Quality of Life Inventory Generic Core Scales, version 4.0 (PedsQL)²¹ were administered. These included parent proxy for all participants below the age of 17 as well as child and adolescent self-report for older children and adolescents. The PODCI was subdivided into the upper extremity, transfer and basic mobility, sports and physical functioning, pain and comfort, happiness and global functioning subscales. Similarly, the PedsQL was subdivided into the physical and psychosocial (emotional, social and school) functioning domains. Established population reference ranges were accessed for the PedsQL, PODCI measures.^{22,23}

eTable 1. Multimodal assessment techniques

Modality	Assessment Technique	
	<17 Years	≥17 Years
Clinical	Modified-pediatric Total Neuropathy Score (ped-mTNS)	Total Neuropathy Score – clinical version (TNSc)
Neurophysiological	Nerve conduction studies	Nerve conduction studies
Functional	Movement Assessment Battery for Children (MABC)	Von Frey monofilaments Grating orientation task Grooved peg board task
Patient-Reported Outcomes	Paediatric Quality of Life Inventory Generic Core Scales (PedsQL) Paediatric Outcomes Data Collection Instrument (PODCI)	European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and chemotherapy-induced peripheral neuropathy questionnaire (CIPN20)

eTable 2. Number of participants <17 years and ≥17 years who had each component of the CIPN assessment with age and gender distributions in each of the groups analysed

Component of neurotoxicity assessment	Age group	Cases N=121 <17yrs = 70 ≥17yrs = 51	Age distribution Median (range)	Gender distribution Male%:Female%	Controls N=73 <17yrs = 24 ≥17yrs = 49	Age distribution Median (range)	Gender distribution Male%:Female%
Clinical*	<17yrs	66	16 (7-47)	54 : 46	23	14.5 (6-37)	58.3 : 41.7
	≥17yrs	47			13		
Neurophysiological*	<17yrs	55	16 (7-47)	53.1 : 46.9	22	16 (6-37)	52.5 : 47.5
	≥17yrs	41			18		
Functional	<17yrs	65	13 (7-16.5)	58.5 : 41.5	**	-	-
	≥17yrs	49	22.5 (17.5-47)	51 : 49	32	24.5 (17-49)	37.5 : 62.5
Patient Reported outcomes	<17yrs	70	13 (7-16.5)	57.1 : 42.9	**	-	-
	≥17yrs	45	23.5 (18-47)	51.1 : 48.9	24	25 (17-56)	58.3 : 41.6

Key: *<17yrs and ≥17yrs analysed together for clinical and neurophysiological measures; **compared to population reference ranges^{14,22,23};

eTable 3. General and neuropathy-specific parent-reported and self-reported outcomes for childhood cancer survivors exposed to neurotoxic chemotherapy and controls

Test parameter	CCS-Ntx Mean [SD]	Controls Mean [SD]	p-Value
Participants <17years	N=64		
<u>PedsQL – parent report</u>			
Physical	-0.4 [1.1] [#]	*	0.01
Psychosocial	-0.8 [1.3]	*	<0.0001
- Emotional	-0.5 [1.1]	*	0.0009
- Social	-0.8 [1.4]	*	<0.0001
- School	-0.7 [1.1]	*	<0.0001
<u>PedsQL – self-report</u>			
Physical	0.1 [0.8]	*	0.57
Psychosocial	-0.3 [0.9]	*	0.02
- Emotional	-0.1 [0.9]	*	0.23
- Social	-0.4 [1.2]	*	0.01
- School	-0.2 [0.8]	*	0.09
<u>PODCI – parent report</u>			
Upper Extremity	0.0 [1.0]	*	0.75
Sports and Physical	-0.4 [1.3]	*	0.008
Pain and comfort	0.0 [1.1]	*	0.88
<u>PODCI – self-report</u>			
Upper Extremity	0.0 [1.4]	*	0.82
Sports and Physical	0.0 [1.0]	*	0.75
Pain and comfort	0.1 [1.0]	*	0.40
Participants ≥17years	N=40	N=25	
<u>EORTC QLQ-C30</u>			
Physical and role function	94.0 [12.4]	99.1 [2.4]	0.02
Psychosocial function	84.2 [15.8]	94.5 [8.8]	0.001
General symptom report	10.2 [13.4]	5.3 [5.0]	0.05
Global QOL	78.4 [16.5]	88.3 [9.3]	0.003
<u>EORTC CIPN20</u>			
Sensory subscale	6.4 [10.9]	1.2 [2.3]	0.005
Motor subscale	6.0 [10.9]	1.9 [3.6]	0.04
Autonomic subscale	7.9 [14.1]	3.3 [6.8]	0.08
Total final score	6.4 [10.4]	1.7 [2.6]	0.009

CCS-Ntx – Childhood cancer survivors treated with neurotoxic chemotherapy; SEM – Standard error of the mean; PedsQL – Paediatric Quality of Life Inventory Generic Core Scales; PODCI – Paediatric Outcome Data Collection Instrument; *compared to population reference ranges; #standard deviations from the population mean; EORTC - European Organisation for Research and Treatment of Cancer quality of life questionnaire (QLQ-C30) and chemotherapy induced peripheral neuropathy questionnaire (CIPN20)

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