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REVIEW

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Chemotherapy-induced peripheral neuropathy biomarkers: current updates, challenges, and potentials

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating condition of peripheral nerve because of chemotherapeutic agent exposure among cancer patients. Despite its relatively high prevalence, to date, there has been no specific or standardized diagnostic criteria for CIPN and establishing diagnosis can be burdensome with significant time and efforts. Therefore, there is a need for an accurate biomarker to aid in early and objective diagnosis of CIPN. Based on the relevant pathogenesis of CIPN, herein we discussed several potential biomarker candidates to be incorporated in the diagnosis of CIPN, ranging from bodily fluid-based biomarker such as neurotrophic factors and neurofilaments, genetic biomarker such as microRNAs, electrophysiologic biomarker such as quantitative sensory testing, and imaging biomarkers such as high-resolution ultrasound and magnetic resonance neurography. We also discussed the strengths and weaknesses of each biomarker type, and future directions to accelerate its translation into routine use in clinical practice.

Keywords CIPN, Biomarkers, Neurotrophic factors, microRNAs, QST, Imaging

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is highly prevalent among cancer patients undergoing chemotherapy. In a meta-analysis, it has been reported to be as high as 68% during the first month of treatment [1]. CIPN can be physically disabling as it is marked by sensibility and motor function impairment, neuropathic pain, ataxia, and other disabilities of the affected individuals [2–4]. CIPN potentially reduce their quality of life and, possibly, their adherence to the subsequent chemotherapeutic regimens [5–8]. However, to date, there has been no specific or standardized diagnostic criteria for CIPN. Establishing CIPN diagnosis varies widely between centers and the clinical evaluation often incorporates exhausting and time-consuming questionnaires [9]. Unfortunately, there has been no reliable and universally accepted quantitative biomarker to aid in early and objective diagnosis of CIPN, although there has been some progress in several areas. Herein we discuss the relevant and contemporary pathomechanisms of CIPN, along with several potential biomarker candidates for CIPN and its future directions to translate it into routine clinical practice.

Molecular mechanisms of chemotherapy-induced peripheral neuropathy

CIPN occurs mainly via two major pathways, i.e., neuroinflammation and altered excitability of peripheral neurons. Platinum-based chemotherapeutic medications such as oxaliplatin, cisplatin, and carboplatin exert its adverse effects toward peripheral nerves in the similar

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way as it induces its main actions on tumor cells [10]. Chemotherapeutic agents primarily induce alterations of intracellular organelles, affect membrane receptors and ion channels, impairing intracellular homeostasis, signaling, and neurotransmission, all of which resulting in neuroinflammation, DNA damage, and axonal degeneration [10].

Chemotherapeutic agents induce mitochondrial damage, thus increasing the reactive oxygen species (ROS) production which leads to oxidative stress. Oxidative stress, in turn, induces cellular impairment and apoptosis by means of bioenergetic failure (via mitochondrial damage), depletion of intracellular antioxidants, biomolecular damage, microtubular damage, activation of ion channels, demyelination, neuroinflammation, and impaired mitophagy [10–14]. Furthermore, it has been found that dorsal root ganglion (DRG) was vulnerable to damage caused by chemotherapeutic agents because it is less protected by blood–nerve barrier [11, 15]. DRG exposure to platinum-based, vinca alkaloids, taxanes, and thalidomide chemotherapeutic agents have been associated with its damage [16–19].

ROS directly damages mitochondria and its function. ROS may activate cellular apoptotic pathways and increase the synthesis and secretion of pro-inflammatory cytokines and mediators, by which it accelerates mitochondrial damage [20–23]. Oftentimes, the resulting mitochondrial damage was irreversible. For instance, oxaliplatin and cisplatin was able to bind to mitochondrial DNA (mDNA). The binding, in turn, impairs mitochondrial DNA replication and transcription, thereby disrupting protein synthesis essential for cellular respiration and metabolism, thus causing mitochondrial and cellular dysfunction [10, 24]. This binding is irreparable since mitochondria does not possess DNA repair mechanism. Another example was mitochondrial dysfunction after vincristine exposure by means of altering mitochondrial Ca^{2+} signaling or vacuolization of mitochondria after exposure to paclitaxel [10, 24, 25]. In addition, paclitaxel also damages mitochondria via several mechanisms, including disruption of mitochondrial iron homeostasis via perturbation of ferroptosis pathway and downregulation of *FIS1*, a gene responsible for mitochondrial fission to maintain cellular energy demands [26].

In addition, ROS was found to directly disrupt microtubules. For instance, taxane-based chemotherapeutic agent was found to bind with β-tubulin of microtubules, inducing over polymerization and impairing normal microtubular function [11, 27–29]. Microtubules are critical to axonal transport and impaired microtubular function may lead to peripheral nerve demyelination and neuronal apoptosis. Other chemotherapeutic agents were also linked to microtubular impairment, including vinca alkaloid which binds to tubulin and interferes with mitotic spindle [27, 28, 30]. Similar mechanism was also found on bortezomib exposure which increases microtubule-associated proteins, thus induces microtubular hyper-stabilization [11, 31] (Fig. 1).

Oxidative stress is also strongly associated with neuroinflammation. Many chemotherapeutic agents can cross the blood–brain or blood–nerve barrier and directly incite neuroinflammation through activation of a stream of pro-inflammatory cytokines and mediators. Chemotherapy-induced neuroinflammation affects central and peripheral nervous system and occurs through activation of both innate and adaptive immune system, including activation of satellite glial cells, Schwann cells, astrocytes, and microglia [32–36]. Exposure to chemotherapeutic agents were well-documented to cause increased levels of pro-inflammatory cytokines and mediators, including IL-6, IL-8, IL-1β, and TNF-α [37–41]. Aberrant pro-inflammatory state was also triggered by suppression of regulatory T (T-reg) cells, further exacerbating the inflammation [42, 43]. In addition, chemotherapeutic agents like vincristine were found to be able to activate CX3CR-macrophages, which leads to activate TRPA1, an ion channel responsible for pain sensation in humans. Vincristine and paclitaxel were also known to increased STAT3-CXCL12 gene promotor binding, inducing upregulation and binding of CXCL12 to CXCR4 which leads to increased chemotaxis and promoting inflammation [10].

The combination of oxidative stress and neuroinflammation also lead to axonal degeneration in the peripheral nervous system. Long-term administration of chemotherapeutic agents was found to damage large myelinated, small unmyelinated nerve fibers, as well as intra-epidermal nerve fibers (IENF). IENF are unmyelinated or thinly myelinated nociceptors responsible for sensation of pain arising from periphery. Exposure to chemotherapeutic agents have been shown to reduce IENF [44]. Although IENF density does not always correlate with duration and dose of chemotherapy, as well as the associated CIPN symptoms [45]. The variable outcomes of chemotherapeutic agents to IENF may be influenced by the methods of IENF quantification, demographics (including age and height of the corresponding innervated area), chemotherapy dose–response relationships, and the variable compensatory regenerative nerve response within the course of chemotherapy exposure [46], all of which had to be further delineated.

Nerve growth factor

Nerve growth factor (NGF) is a neurotrophic factor which promotes growth and survival of peripheral sensory nerve cells, sympathetic nerves, as well as the

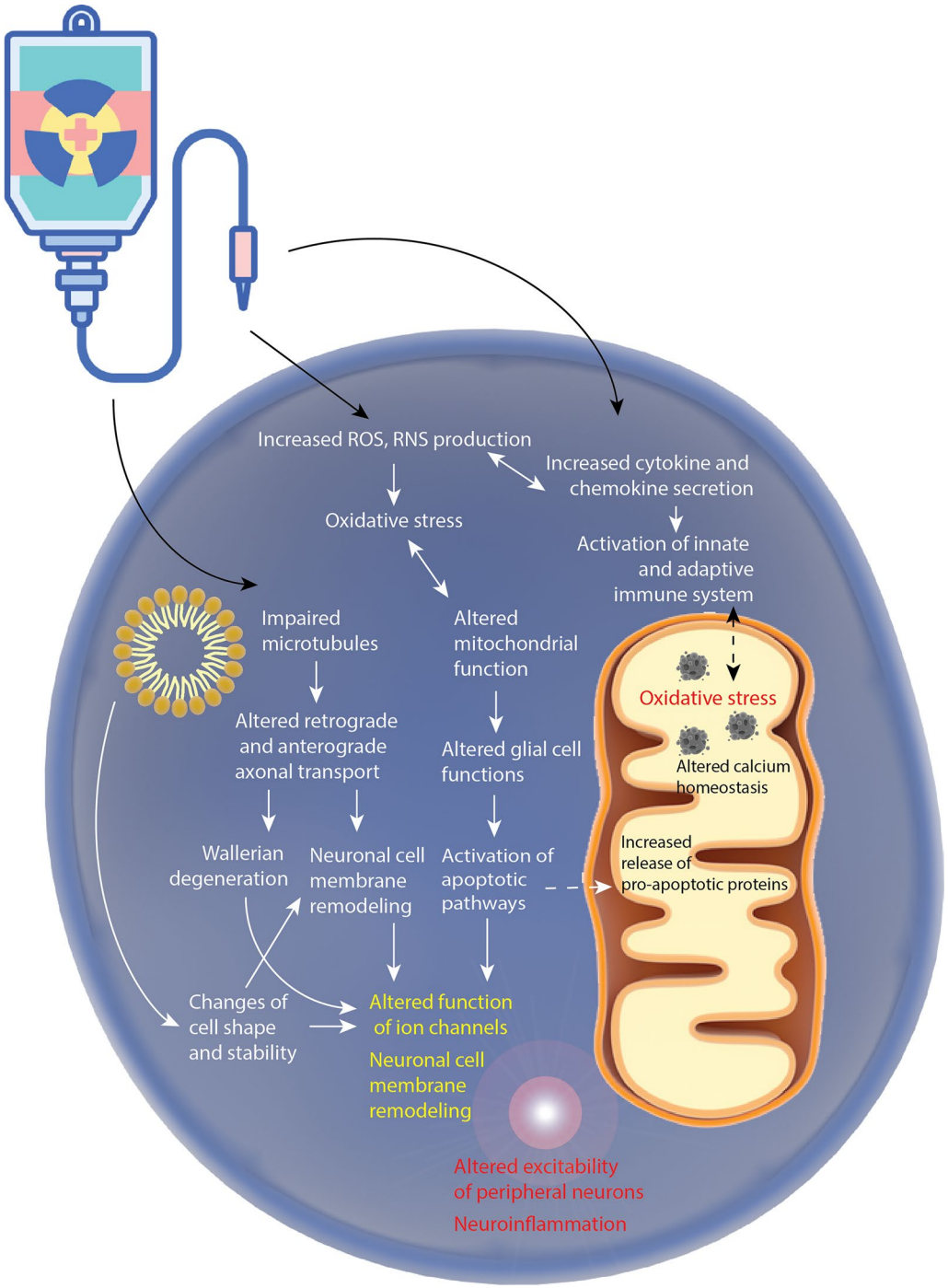

Fig. 1 Relevant pathomechanism of CIPN with respect to the development of suitable biomarker candidates (adapted from Starobova and Vetter [10])

functional integrity of the cholinergic neurons in the central nervous system (CNS) [47, 48]. The seminal study by De Santis and colleagues [49]. had discovered lower circulating NGF levels among subjects receiving platinum-based and taxane-based chemotherapy, by which some patients had undetectable NGF levels after prolonged treatment. Furthermore, the study also found that NGF levels decrement correlated with the severity of chemo-induced toxicity. Similarly, several studies also confirmed these findings. Subjects who received chemotherapy were

generally found to have lower NGF levels when compared to control. This comprises those with hematological malignancies who had received bortezomib, thalidomide, and vincristine, or those with multiple myeloma who had received bortezomib [50, 51]. In a study involving women with cervical cancer receiving paclitaxel and cisplatin, with or without ifosfamide, NGF levels had a significant negative correlation with the severity of CIPN [52]. In addition, a clinical study involving 60 subjects with colorectal, gastric, or lung cancer receiving taxane, platinum or bortezomib chemotherapy demonstrated increased NGF levels among those with painful CIPN [53]. Moreover, those subjects did not demonstrate significant loss of intra-epidermal nerve fiber density, suggesting a weak correlation between structural nerve fiber changes and NGF levels. However, the study did show a different NGF trajectory level (high vs. low in the previously mentioned studies), partly of which could be explained by the inclusion of mixed chemotherapeutic agents used (including oxaliplatin), different measurement time points (putting coasting phenomenon into consideration), and different criteria for establishing CIPN severity.

In addition to functioning as a screening or diagnostic tool for CIPN, NGF levels were also reported to be higher after vitamin B administration among subjects who suffered from peripheral neuropathy after bortezomib therapy when compared with control groups [51], suggesting its effectiveness as a biomarker for monitoring treatment success and perhaps, prognosis.

The possible mechanistic interaction of NGF and CIPN was perhaps due to its high affinity to NGF receptor, tropomyosin-related kinase receptor A (TrkA) which are richly expressed in the dorsal root ganglion (DRG) neurons, which in turn able to regulate the impact of chemotherapy-induced neuronal toxicity [9, 54]. Nevertheless, the pragmatic use of NGF as a blood-based biomarker for CIPN requires further studies, particularly those which attempt to delineate the mechanistic and temporal relationships between the two, with a precise and standardized diagnostic criteria of CIPN, along with its progression.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is also an NGF that possesses a central role in the development, maintenance, and repair of the CNS and the peripheral nervous system (PNS). BDNF is synthesized exclusively in humans and specifically binds to tropomyosin-related kinase receptor B (TrkB) and non-selective low-affinity TNF-α-related p75 (p75 NTR) neurotrophin receptor. There are few clinical studies evaluating the relationship of BDNF and CIPN. One study evaluated 91 multiple myeloma patients receiving bortezomib and/or thalidomide and found a significant correlation between BDNF levels and the severity of polyneuropathy and BDNF levels also determined chemotherapeutic treatment responses. Interestingly, this study provided a diagnostic sensitivity and specificity of BDNF levels for diagnosing CIPN (76 and 71%, respectively) [55]. Another study involved 45 multiple myeloma patients receiving vincristine or bortezomib and have their BDNF levels and single nucleotide polymorphism (SNP) for valine-to-methionine substitution at codon 66 (Val66Met) checked, along with an established diagnosis of CIPN via Total Neuropathy Score (TNSr) and FACT-GOG-NTx [56]. The study found that low pre-treatment serum BDNF levels significantly correlated with CIPN development and vice versa, and that development of CIPN was associated with depression among subjects with Met/Met genotypes. Interestingly, authors believed that Val66Met did not affect BDNF signaling but impaired cellular distribution and dysregulation of BDNF [56, 57]. Furthermore, platelet's BDNF secretion was thought to be impaired by chemotherapeutic agent such as bortezomib, thus reducing its capacity to repair the damaged peripheral nerves [58, 59]. In addition, the administration of pro-neurotrophic agent such as 2-pentadecyl-2-oxazoline of palmitoylethanolamide (PEA-OXA) to rats with oxaliplatin-induced peripheral neuropathy was able to reduced hyperactivation of glial cells, increased production of pro-inflammatory cytokines in the dorsal horn of spinal cord, and upregulation of neurotrophic factors (including BDNF) in the DRG [60]. The authors believed that increased BDNF levels was associated with structural as well as functional improvements in CIPN. Hence, BDNF levels can potentially be used as a screening tool, prognostication, and to monitor disease progression and therapeutic benefits.

However, again, the potential use of BDNF as a blood-based biomarker for CIPN warrants further studies as there was a discrepant association between BDNF levels and the severity of CIPN symptoms between two study groups [55, 56]. One author explained several underlying reasons for this discrepancy, comprising different cancer-dependent BDNF secretion levels (particularly those of hematologic vs. non-hematologic malignancies), different criteria used for the diagnosis of CIPN, and the absence of any objective measurements to address CIPN, such as quantitative sensory testing (QST) or alternatively, by using small-fiber testing using Q-sense device [61, 62]. An obscure temporal and mechanistic relationships between BDNF levels and the natural history of CIPN itself may preclude its definitive and routine use in CIPN, be it as a screening tool, prognostication, or to monitor disease progression and therapeutic benefits.

Neurofilament proteins

Neurofilaments (NF) are intermediate filaments primarily expressed by large, myelinated axons and will be secreted into the CSF during neuron or synaptic degeneration. NF can be classified into three categories according to its molecular weight, i.e., light (NF-L), medium, or heavy chain (NF-H). NF levels can be detected on ultra-low concentration in the blood or corresponding injured tissue, thus ensuring its sensitivity [9]. NF-L has been studied in animal model, that is using rat model exposed to vincristine. NF-L levels of rats exposed to vincristine demonstrated a fourfold increase as opposed to controls, in parallel with signs of axonopathy and IENF loss [63]. Another study has also confirmed these findings, wherein exposure to cisplatin and paclitaxel increased NF-L levels and that its increment was associated with severity of morphological and functional alteration of axonal structure, suggesting its reliability in detecting CIPN and linear association between CIPN signs and symptoms as well as its morphological changes [64]. In addition, NF-L has also been studied among human patients receiving oxaliplatin and monitored for oxaliplatin-induced peripheral neuropathy (OAIPN). NF-L levels were significantly higher among those with more severe OAIPN and that its levels markedly decrease 6 months after cessation of chemotherapy [65]. Another study also observed NF-L levels to increase linearly with CIPN severity and that its levels are markedly lower among asymptomatic individuals as opposed to those with active symptoms, indicating the dynamic and linear association of NF-L levels with disease progression and severity, thus highlighting the usefulness of NF-L to detect early CIPN and monitor the ongoing neuroaxonal injury [66]. However, it was reported that NF-L had poor accuracy in defining CIPN according to one clinical study involving breast cancer patients treated with chemotherapy [67]. The authors suggested that CIPN involves a more distal portion of peripheral nerves rich in dendrites as opposed to axons. Regardless, further studies are required to fully elucidate NF roles and natural responses in the event of CIPN (Fig. 2).

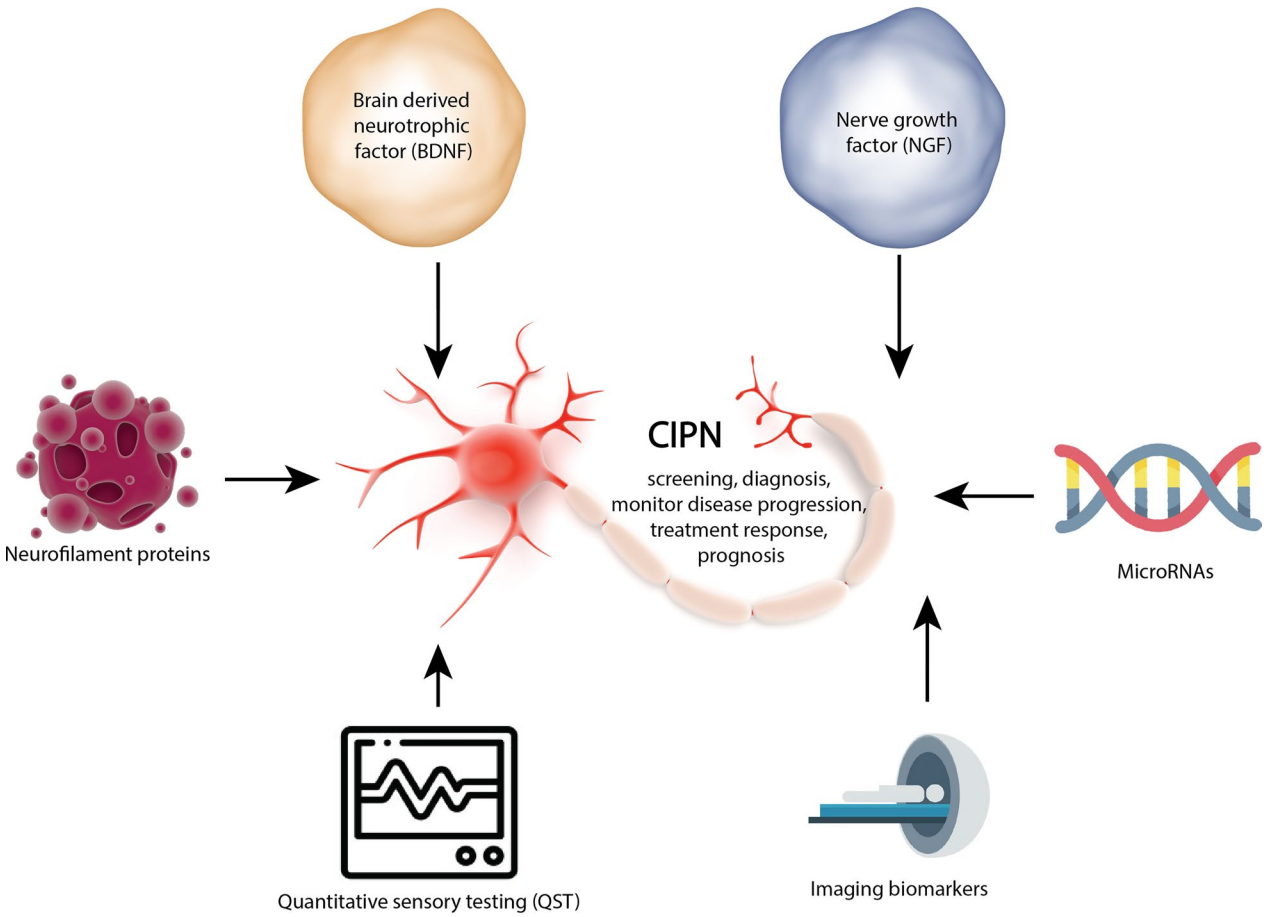

Fig. 2 Multiple candidate biomarkers potentially used to aid screening, diagnosis, to monitor disease progression, treatment response, and prognostication of CIPN [49, 55, 65, 68–70]

MicroRNAs

MicroRNAs (miRNAs) are endogenous, single-stranded small RNA with length of approximately 22 nucleotides which function as antisense RNA to regulate target genes post-transcriptionally [71]. The association between miRNAs and genes are somewhat minute but significant as a single gene can be simultaneously targeted by several miRNAs, whereas a single miRNA may target multiple genes [72]. MiRNAs consist of a highly complex network with their gene targets [71]. MiRNAs' active role has been found in both physiological as well as pathological processes, including cancer [73]. Many studies have confirmed the extent of miRNAs involvement in various aspects of cancer, including its proliferation, differentiation, apoptosis, metabolism, invasiveness, metastatic preponderance, and resistance to chemotherapy [68].

The potential use of miRNAs for the diagnosis of CIPN was studied. An in vivo animal model with paclitaxel-induced CIPN demonstrated significantly increased levels of miR-124 (i.e., 5- and 10-fold on day 8 and 16, respectively) [74]. The increased miR-124 expression levels were associated with cold allodynia and axonal degeneration of DRG and sciatic nerve, indicating its significant role in the pathogenesis of CIPN. Indeed, miR-124 is one of the many miRNAs associated with neuronal cell activity, wherein its plasma levels increment was reported in CNS injury, such as stroke [75]. In addition, miR-124 was also shown to regulate microglial function and that miRNA-124-3p was able to attenuate allodynia and thermal hyperalgesia by means of regulating Egr1 expression in the DRG and dorsal horn of spinal cord [76, 77].

There was one clinical study involving 84 patients with severe and mild CIPN after receiving paclitaxel for breast cancer [78]. There were 15 miRNAs with |fold change| > 0.5, of which miR-451a demonstrated the highest fold change, although statistically insignificant ($P = 0.103$). MiR-451a is associated with metabolism of paclitaxel, i.e., regulating the expression of drug transporter protein (P-glycoprotein), thus plays a central role in resistance to chemotherapy. Furthermore, there were 14 combinations of three miRNAs ranging in accuracy of 50 to 78.6%. However, the potential use of miRNAs as CIPN biomarker is rather a long shot due to multiple reasons. Firstly, most of the identified miRNAs did not have high fold change, not to mention its statistical insignificance. This is reasonable since most of them do not possess direct mechanistic association with CIPN. For instance, among the 14 miRNAs, one of them was responsible for angiogenesis and another was useful in distinguishing early-stage pancreatic cancers, a somewhat typical loose association and rather generic role of many miRNAs. Secondly, validation of significant miRNAs requires a large pool of sample size and should have enough discriminatory powers with respect to demographics, health and disease status, and other confounding factors [71]. Thirdly, there should be a clear establishment of different types of miRNAs involved within the natural history continuum of CIPN. For instance, there were roughly 25 different miRNAs clustering in early, progressing, and late non-small cell lung cancer at diagnosis, treatment selection, and its prognosis [71]. The last criterion is critically important to ensure the accurate and prudent use of miRNA as a screening tool, prognostication, or to monitor disease progression and therapeutic benefits.

Various attempts have been made to bolster the diagnostic power of miRNAs toward certain diseases. For instance, there is an ongoing trend to combine several miRNAs or incorporation with other classic biomarkers. Others utilized bioinformatics or computational approach to better sort and calculate the complex array of miRNAs and its associated target genes. In fact, bioinformatics approach was used to address significant genes involved in platinum-induced neuropathy and combined taxane–platinum-induced neuropathy according to its number of connections.

Quantitative sensory testing (QST)

QST is a standardized psychophysical test to measure multiple sensations, including vibration sensation, mechanical detection thresholds, and thermal (cold and heat) detection thresholds [79]. QST has the upper hand of being non-invasive, objective, and yields personalized results for each individual. QST is also able to detect subclinical pathological changes that might otherwise be regarded as normal when tested using a more conventional electrodiagnostic approach, such as nerve conduction studies [80]. The latter is particularly relevant in the case of small-fiber neuropathy, including CIPN, primarily in the early phase of the disorder [81, 82]. There were numerous studies employing QST for the purpose of CIPN detection. For instance, one study evaluated two clinical trials involving solid tumor survivors had found that those with moderate-to-severe CIPN had markedly impaired tactile, vibratory, and thermal thresholds compared to patients without CIPN, and that patient-reported outcome was correlated with QST results [69]. Another study evaluated the impact of oxaliplatin on peripheral neuropathy with QST and found prolonged pegboard test completion time, elevated bumps detection threshold, increased touch detection threshold, and increased warm detection threshold among those with increasing cumulative dose of oxaliplatin [83]. The diagnostic profiles of each QST component varies considerably, depending on the type of chemotherapy used, measurement time point, and the methods employed

for QST. For instance, vibration detection threshold measured among subjects receiving oxaliplatin to detect clinically significant neuropathy 6 months after treatment demonstrated sensitivity and specificity of 76% and 53%, respectively [84]. Another study which evaluated the impact of oxaliplatin and cisplatin treatment among colorectal cancer patients using QST found that a change of −0.05 °C of cold detection threshold had a sensitivity and specificity of 92.3% and 64.9% in detecting CIPN after 6 months of chemotherapeutic treatment, whereas a change of −0.85 °C of heat detection threshold yielded a sensitivity and specificity of 64.3% and 70%, respectively [85].

In addition, QST can also be used to distinguish different types of CIPN, mainly neuropathic vs. non-neuropathic pain. For instance, one study evaluated the sensory phenotypes of taxane-induced peripheral neuropathy (TIPN) among breast cancer patients [86]. Those with neuropathic pain symptoms had normalized heat pain thresholds when examined using QST, thus indicating retained C-fiber and TRPV1 function. Recently, one study successfully utilized diode laser fiber-type selective stimulator (DLss) to selectively stimulate C and Aδ fibers, as determined by C/Aδ ratio, to detect painful CIPN on its earliest phase [87]. The resulting classification based on CIPN symptoms may potentially be used to monitor disease progression, determining the temporal relationship between symptoms with pathological process of CIPN in various time points, and to monitor treatment response and prognosis. In fact, several studies had incorporated QST profiles with patients' response to medications for various types of neuropathic pain [88, 89].

However, the use of QST may be used with caution due to the wide normal range (thus increasing the false-negative rate), highly variable measurement methods, requires full patient cooperation and attention (inattentive individuals may increase erroneous results), as well as inability to distinguish malingering cases [90, 91]. Considering CIPN, there should be a well-defined diagnostic criterion, both in terms of clinical symptoms and QST thresholds for each of its component.

Nerve conduction studies

The use of conventional nerve conduction studies (NCS) has generally been limited by low sensitivity in the case of small-fiber neuropathies such as CIPN. It is obviously due to the relative nature of the small nerve diameter, non-myelinated, with miniscule axonal dimension resulting in too low of conduction velocities and amplitudes to be able to be detected by the NCS device [92]. However, NCS when applied appropriately, may yield important cues to nerve damage associated with CIPN, albeit with varying degree of significance. Several studies had found early SNAP decrease preceded CIPN among asymptomatic individuals with prior exposure to chemotherapy [93–95]. In fact, one observational study using NCS confirmed that a more severe damage was found among sensory than motor nerves among CIPN patients at different stages of chemotherapy, although it had a low association with clinical symptoms [96]. Another study investigated the impact of platinum and taxane-based chemotherapy toward CIPN using NCS and found markedly lower amplitude of SNAP and CMAP, with platinum-based chemotherapy caused a more profound CMAP decrement of ulnar and tibial nerve [97]. However, when combined with clinical symptoms (i.e., using total Neuropathy Score), the model did not show statistical significance. Moreover, one study from Japan took even further steps that it used point-of-care NCS, a relatively quick and easy-to-use device to do NCS which found significant decrease of SNAP and preservation of conduction velocities as CIPN progressed [98], further confirmed axonal degeneration resulting from chemotherapy exposure. The potential of NCS in detecting CIPN is thus worth revisiting and might be combined with other related modalities such as QST to yield better diagnostic sensitivity.

Imaging biomarkers

Neuroimaging can potentially be used as a biomarker for CIPN. One can measure the cross-sectional area (CSA) of the affected nerve by using high-resolution ultrasound (HRUS) [99]. One study evaluated the effect of taxane chemotherapy against the CSA of tibial motor nerve, median motor nerve, and sural sensory nerve and compared the results with healthy controls. The study also examined the intra-epidermal nerve fiber density (IENFD) of the corresponding patients. It was found on HRUS that sural nerve of those who had received chemotherapy was 1.2 mm^2 smaller than healthy controls, and that decreased nerve CSA was associated with decreased IENFD by a ratio of 1 mm^2: 2.1 nerve/mm [70]. On the contrary, one study which evaluated the impact of oxaliplatin, irinotecan, and 5-fluorouracil (FOLFIRINOX) had found an increased CSA of tibial and fibular nerve using HRUS, and that there were no correlations between CSA size, electrophysiologic findings, or clinical severity [100]. The increased CSA at entrapment sites may indicate oxaliplatin-induced nerve susceptibility to mechanical damage, even when there was no neurophysiologic evidence of entrapment [101].

Magnetic resonance neurography (MRN) had also been evaluated as a potential neuroimaging biomarker for CIPN. It has been previously used as a biomarker for other peripheral neuropathies, including diabetic neuropathy and HIV-associated neuropathy [102]. There was a significant DRG hypertrophy in oxaliplatin-induced

peripheral neuropathy patients as measured using MRN and that it correlated with the sensory neuropathy [103]. Recently, diffusion tensor imaging (DTI) was employed for early diagnosis of CIPN, demonstrating correlation between fractional anisotropy (FA) and apparent diffusion coefficient (ADC) at medial and left plantar nerve [104]. The evidence for MRN is robust on proof-of-concept ground, although its integration into clinical practice requires further studies.

Artificial intelligence and machine learning

Artificial intelligence (AI) has been extensively incorporated and studied for the advancements of diagnosis and treatment of various disorders. In the field of cancer, AI has been proven useful to aide chemotherapeutic drug research and development (e.g., identifying new drug compounds or improving drug delivery effectiveness and its permeability), predicting treatment response, as well as assisting in clinical decision support system [105]. Recently, AI also has shown promise in the detection and prevention of CIPN prior to drug exposure. For example, one study used machine learning-based quantitative-structure toxicity relationship models, i.e., computational models to detect chemotherapeutic drug toxicity (i.e., CIPN) among novel antineoplastic drug candidates with satisfactory results, and the system even able to stratify drugs' risk (high, medium, low) in inducing CIPN [106]. Another study used machine learning using input from electronic health records data and compared three algorithms to develop prediction models and found that logistic regression yielded the highest and sufficient AUC (0.62–0.83) compared to decision tree and artificial neural network [107].

Conclusions

Given the account of the relatively high prevalence of CIPN and absence of any predictive biomarker for the purpose of early diagnosis, prognostication, or to monitor disease progression and therapeutic benefits, the existence of such biomarkers is regarded highly necessary. There are several problems, at least in our sight, that needs to be addressed. Firstly, there should be a standardized definition and diagnostic criteria for CIPN, whereby there are a plethora of discrepancies in defining CIPN, including the use of multiple patient- or examiner-based questionnaires, lack of nerve conduction study protocols for CIPN and the resulting underutilization of the examination thereof. Inability to define CIPN universally has been proven to be problematic as it encourages varying research methods and, thus varying outcomes, resulting in inconclusive findings.

Secondly, there should be a clear temporal and mechanistic relationships between various chemotherapeutic agents in inducing CIPN, along with the candidate biomarker profiles during the natural course of CIPN. For instance, there has not been a clear pathomechanism regarding the coasting phenomenon induced by platinum-based chemotherapy, or the contradictory rise and fall of nerve growth factors, including NGF and BNDF, along the course of CIPN and that by artificially replacing these growth factors (e.g., NGF) during the depletion phase was proven to be ineffective in ameliorating CIPN or worse, even exacerbated the pain severity, or the variable impacts of multiple chemotherapeutic agents with its corresponding dose–response relationship toward IENFD, and that NGF levels do not correlate with IENFD in spite of both reflects nerve degeneration and regeneration phases. These first two factors needed to be addressed simultaneously by conducting longitudinal clinical studies which attempt to incorporate and characterize potential biomarker candidates along with the natural history of CIPN which was preceded by a confirmed diagnosis using universally accepted diagnostic criteria. In fact, one longitudinal clinical multicenter study called Genetics and Inflammatory Markers for CIPN (GENIE) is attempting to solve this issue by incorporating genomic, metabolites, DNA methylation, gene expression, cytokines, and chemokines before, during, and 12 months after taxane treatment among 400 patients with breast cancer. The combined biomarker monitoring results will be compared with multiple CIPN assessment tools, including CTCAE, EORTC CIP20, BPI-SF, and PROMIS. Given the broad spectrum nature of the study, it hopefully may be able to capture the natural history of CIPN along with association to multiple biomarkers of each stage more robustly. Moreover, the authors employed machine learning to detect non-linear relationships among variables, thus reinforcing the diagnostic and prognostic sensitivity of the study [108] (Fig. 3).

Diagnosing CIPN requires a multidimensional approach, by which it incorporates the subjective symptoms, clinical signs (e.g., reduced vibratory perception or the presence of motor weakness), supporting electrodiagnostic findings, and, potentially, quantitative biomarkers. CIPN diagnosis also requires a thorough understanding of its natural history and phases, thus encouraging one to put CIPN into a disease continuum. The diagnostic approach, therefore, should follow the path of those neurodegenerative diseases, like Alzheimer's disease (AD) for example, and less of toward disease with simple diagnostic cut-off using blood-based biomarker, such as diabetes mellitus, wherein diagnostic confirmation, monitoring treatment response, as well as prognostication can be done using a clear cut-off point of plasma glucose levels. In AD, the currently accepted diagnostic criteria established by National Institute on Aging (NIA) and

Fig. 3 Several critical key points needed to be addressed to better diagnose and treat CIPN

the Alzheimer's Association (AA) has already incorporated biomarkers including neuroimaging-based (MRI or PET scan [amyloid, Tau, or FDG]) and bodily fluid-based (CSF beta-amyloid levels), as well as the classification of AD diagnosis based on disease continuum, from preclinical to dementia due to AD [109, 110]. Although the corresponding diagnostic criteria is reserved to facilitate research, there is an ongoing trend to incorporate it into routine clinical practice [111]. Such an approach has the upper hand to study the natural history of AD in a complete picture, the temporal and mechanistic relationships of biomarker candidates along AD natural course, standardizing clinical study outcomes, from biomarkers to clinical trials, and potentially accelerating the findings of disease-modifying drugs with clinical significance. Given the dramatic progress in AD research in recent years, for instance, marked by the first ever approval of disease-modifying monoclonal antibodies, aducanumab for the treatment of AD by FDA [109], regardless of its controversy [112], it is prudent to assume that one of which may be contributed by the utilization of NIA-AA AD diagnostic criteria. In our opinion, the same approach should also be applied to CIPN.

Abbreviations

CIPN	Chemotherapy-induced peripheral neuropathy
microRNAs	Micro ribonucleic acids
QST	Quantitative sensory testing
DNA	Deoxyribonucleic acid
ROS	Reactive oxygen species
DRG	Dorsal root ganglion
mDNA	Mitochondrial DNA
IL	Interleukin
TNF-α	Tumor necrosis factor alpha
T-reg	Regulatory T
CX3CR	Chemokine receptor type 3
TRPA1	Transient receptor potential cation channel, subfamily A, member 1
CXCL12	C-X-C motif chemokine ligand 12
CXCR4	Chemokine receptor type 4

IENF	Intra-epidermal nerve fiber
NGF	Nerve growth factor
CNS	Central nervous system
TrkA	Tropomyosin-related kinase receptor A
BDNF	Brain-derived neurotrophic factor
PNS	Peripheral nervous system
TrkB	Tropomyosin-related kinase receptor B
p75 NTR	Low-affinity TNF-α-related p75
SNP	Single nucleotide polymorphism
TNSr	Total Neuropathy Score
PEA	Palmitoylethanolamide
NF	Neurofilament
OAIPN	Oxaliplatin-induced peripheral neuropathy
CSA	Cross-sectional area
HRUS	High-resolution ultrasound
IENFD	Intra-epidermal nerve fiber density
MRN	Magnetic resonance neurography
ADC	Apparent diffusion coefficient
AD	Alzheimer's disease

Author contributions
A.S. and I.P.E.W. drafted the manuscript. I.P.E.W. proofread the final draft of the manuscript, A.S. formatted the manuscript in accordance to The Egyptian Journal of Neurology, Psychiatry, and Neurosurgery style.

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Consent for publication
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Competing interests
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Publisher's Note

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