Prevention and Management of Platinum Compounds-Induced Neurotoxicity

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Abstract

Oncologists considered platinum-based medicines as potent cytotoxic agents. Despite their efficacy in combination chemotherapy regimens for many solid tumors, they have many substantial side effects that limit their use. There is no known prophylactic strategy for platinum drugs-induced neurotoxicity, which limit a therapeutic dose benefit. This review highlights the etiology of platinum-drugs-induced neuropathy, and covers the preventative and therapeutic options for cancer patients. It focuses on clinical studies conducted between 2010 and 2020. Loss of functional indications such as touch, vibration and joint location, as well as diminished or missing deep tendon reflexes in the upper and lower limbs are all markers of neurotoxicity. These side effects may last for months or years after treatment, lower quality of life, and creating a substantial survivorship issue. DNA damage, oxidative stress, mitochondrial dysfunction, dysregulation of intracellular signaling, impairment of voltage gated ion channel function, and neuro-inflammation have all been proposed as mechanisms for chemotherapy-induced peripheral neuropathy (CIPN). There are no proven pharmaceutical or nutritional therapies to prevent CIPN. Several anti-CIPN medications have been investigated, but either had no effect or had an effect in a limited sample study. Supportive care medications such anti-epileptic and antidepressants are used to treat CIPN.

Keywords: Peripheral neuropathy, Platinum compounds, Neurotoxicity, Chemotherapy

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INTRIDUCTION

Platinum-based drugs are among the most powerful cytotoxic agents in the field of oncology [1]. Cisplatin is the first platinum-based drug, since its introduction in the 1970s, following Rosenberg’s discovery of its anti-proliferative properties, platinum-based chemotherapy agents have been used for treating cancer [2]. Following that, many platinum compounds have been produced, and among all of these compounds thirty-five have shown sufficient pharmacological benefits [3]. The newer platinum derivatives, such as carboplatin which is a platinum medicine of the second generation that has similar activity to cisplatin in certain cancer forms, and oxaliplatin which is a platinum drug of the third generation, have also been commonly used in oncologists’ practices [4]. Despite their effectiveness as a critical component of combination chemotherapy regimens against large numbers of solid tumors such as cancers of the lung, testes, ovary, cervix uteri, head and neck, colon, and rectum; platinum compounds have a variety of significant adverse effects that restrict their use. Although some of the platinum-based chemotherapeutic side effects like myelosuppression and nephrotoxicity can be minimized, neurotoxicity remains a significant dose-limiting side effect for which no established preventative strategy exists, thus limiting the potential therapeutic effect. Chemotherapy induced neurotoxicity could also persist after treatment completion for months or even years thereby reducing the quality of life and posing a significant survivorship problem [5,6]. While platinum compounds have some structural similarities, they differ significantly in terms of clinical application, pharmacokinetics, and adverse effect profiles [1]. Carboplatin induced neurotoxicity is minor in comparison to cisplatin and oxaliplatin neurotoxicity, although it may occur when large doses are used; it usually required a 10-fold higher drug concentration than cisplatin to achieve a comparable level of cytotoxicity. This occurs because cisplatin and oxaliplatin both cause an increase in reactive oxygen species production and 8-oxoguanine DNA damage, while carboplatin does not induce that [7]. Therefore, cisplatin conventional therapy or oxaliplatin-based therapies will sometimes cause intolerable neuropathic symptoms, restricting their use at the most appropriate levels and for the longest period [8]. The aim of this review was to highlight the pathogenesis of peripheral neuropathy which induced by using chemotherapeutic drugs. This review also addressed the prevention and treatment approaches available to minimize its adverse effects on cancer patients. It primarily described the clinical trials that have been carried out in the period between 2010 to 2020.

Literature search

The current review was focusing on the chemicals and medications that can be used to prevent and treat platinum compound-induced neurotoxicity. The Google scholar, PubMed, and the Science Direct database were searched and the reference lists of the relevant article were screened. The following keywords were used: “platinum compound”, “toxicity”, “neurotoxic”, “neurotoxicity”, “neurotoxic effect”, “treatment”, “peripheral neuropathy”. Selected article was limited to the period from 2010 to 2020. The review mostly included clinical trial studies and few preclinical animal studies to retrieve information relevant to the mechanism of neurotoxicity of platinum compounds.

Pathogenesis of neurotoxicity induced by platinum compounds

Many different mechanisms for platinum-based chemotherapy drugs inducing CIPN have been suggested (Figure 1), which include the following:

Figure 1: Platinum-induced neurotoxicity molecular pathways. Platinum medicines reach sensory neurons via simple or enhanced diffusion via copper transporters OCT1, OCT2, and CTR1. Once inside the neuron, they link nuclear and mitochondrial DNA. The nuclear DNA adduct promotes the BER and NER processes while inhibiting transcription. However, it enhances Ape-1 protein production, which induces p53 induction, cytochrome C release from mitochondria, and caspase-3 activation. All of these variables, plus apoptotic pathway dysregulation, cause neuronal death. Mitochondrial DNA adducts inhibit mitochondrial replication and function. This reduces ATP and increases ROS. Proteins, lipids, and DNA will be extensively oxidized. The loss of antioxidant reserves due to platinum drug reactive forms enhances ROS levels [9].

DNA damage along with mitochondrial damage

The main target of platinum-based chemotherapy induced peripheral neurotoxicity is the sensory neurons of the dorsal root ganglia (DRG), and the key triggering mechanism for chronic DRG neuron damage is the binding of platinum drugs to DNA, which can eventually lead to apoptosis due to aberrant reentry into the cell cycle.
pathway [10]. Apoptosis of dorsal root ganglia (DRG) neurons that occur as a consequence of oxidative stress; mitochondrial dysfunction; the development of DNA adducts; and intrastrand and interstrand DNA and DNA-protein cross-links (which disrupt DNA base excision repair and transcription), will result in a non-length-dependent sensory neuropathy (or ganglionopathy), which is a clinically distinct phenomenon from other types of peripheral neuropathy induced by other chemotherapeutic agents in that it has a length-dependent or stocking and-glove pattern [11]. Furthermore, there is evidence that not only nuclear DNA is damaged, but also mitochondrial DNA is bound and damaged, which may explain longer-term neuronal harm in patients with platinum-induced peripheral neurotoxicity (PIPN) [11].

**Intracellular signaling Dysregulation**

There are many different intracellular signaling pathways through which platinum causes unlimited proteolysis. Disruption of intracellular Ca\(^{2+}\) is linked to CIPN, fluctuations of Ca\(^{2+}\) concentration can affect membrane excitability, neurotransmitter release, and gene expression [12]. Furthermore, protein kinases and caspases as the second messenger signaling molecules can cause axonal degeneration [13].

**Impairment of voltage gated ion channel function**

Platinum compounds, especially oxaliplatin have inhibitory effects on the neuron voltage-gated sodium (Na\(^+\)) channels. They significantly delay their inactivation and lowers the peak Na\(^+\) current, resulting in a longer relative refractory period for sensory neurons. This hyper excitability state of Na\(^+\) channel will result in spontaneous ectopic discharges. On voltage-gated Na\(^+\) channels, oxaliplatin may have isoform-specific effects, resulting in unusual neuropathy symptoms including cold-aggravated peripheral pain [14]. It can also have an indirect effect on Na\(^+\) channels by chelating outer membrane calcium ions through its metabolite oxalate. It had been also found that oxaliplatin has an antagonistic effect on neuronal fast and slow potassium channels resulting in action potential broadening and repeated firing [15]. Unlike oxaliplatin, cisplatin has no remarkable impact on sodium or potassium channel activity in neurons, but instead it tends to reduces calcium channel currents, especially in small-diameter neurons of the rat DRG [16].

**Inflammation of neuron**

It has been found that CIPN is linked to an increase in pro-inflammatory cytokines (tumor necrosis factor- interleukin (IL)-1, and IL-6) and a decrease in anti-inflammatory cytokines in the DRG and spinal cord. Immune cell infiltration and activation in the neuron are the features of neuroinflammation, the process accompanied by formation of cytokines and chemokines by peripheral and central glial cells [17].

**Symptoms of platinum induced neuropathy**

Acute and chronic peripheral neurotoxicity are both classified as PIPN, with the latter being associated with all platinum-based compounds and the former being limited to oxaliplatin (acute and chronic neurotoxicity occur in 85% and 73% of the patients, respectively). Sensory neuropathy (or ganglionopathy) with anterograde non-length-dependent neuronal degeneration is the most common symptom of chronic peripheral neurotoxicity. Furthermore, symmetrical glove and stocking sensory loss, burning sensations and axonal neuropathy are also chronic neuropathic symptoms that may occur in 50% to 70% of patients [8,18]. Both positive sensory symptoms (tingling, numbness, paresthesia, neuropathic pain) and loss-of-function signs (reduction or loss of sensation to touch, vibration, and joint location with decreased or absent deep tendon reflexes) are common in both the upper and lower limbs. If the patient receives treatment for a long enough period of time then neuropathy will spread to other body segments in anon-length-dependent fashion, resulting in sensory ataxia [19]. In extreme cases motor and autonomic symptoms may also occur [20]. During chemotherapy, sensory symptoms were more pronounced in the hands than in the feet; however, by 18 months, sensory symptoms were more intense in the feet as compared to the hands [21]. Progressive and unstoppable hearing loss and tinnitus are typical side effects of platinum-based chemotherapy in children, and they occur more frequently with cisplatin (60% of children) than with oxaliplatin [22]. Oxaliplatin is unusual in that it causes acute neurotoxicity in the form of cold-induced dysesthesias. This acute dose-independent neurotoxicity may occur in up to 90% of patients during or shortly after oxaliplatin infusion, and it is usually characterized by intermittent cold-induced paresthesia and dysesthesias targeting the distal extremities, perioral, and pharyngo-laryngeal regions which typically resolves before the next oxaliplatin cycle [23]. Generally, platinum-induced neurologic symptoms become apparent when such accumulated drug doses have been administered. For example, the threshold values for neurotoxicity growth have been established at 350 mg/m\(^2\) for cisplatin and 550 mg/m\(^2\) for oxaliplatin, respectively [6].

**Diagnosis of platinum induced peripheral neuropathy**

The Functional Assessment of Cancer Therapy (FACT)-Taxane scales, the Patient Neurotoxicity Questionnaire, the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire [QLQ] to measure chemotherapy-induced peripheral neuropathy, and the EORTC QLQ C30 questionnaire are neurotoxicity scoring systems utilized for the evaluation of effect of chemotherapy-induced neurotoxicity on the quality of
patient’s life [24]. Furthermore, the scale developed by the Eastern Cooperative Oncology Group and the National Cancer Institute-Common Terminology Criteria (NCI-CTC) is considered to be among the different toxicity grading scales used for peripheral neurotoxicity assessment [25]. Nerve conduction velocity studies and electromyography are the global standard neurophysiological methods for detecting the position and degree of neurological damage caused by platinum drug treatment. A sensitive, easily accessible and precise endpoint of acute oxaliplatin-induced motor nerve hyperexcitability is objective electromyography examination of the motor nerve techniques which is used for measuring axonal excitability, it implies that axonal voltage-gated Na+ channels in motor and sensory axons are malfunctioning [26].

**Patient’s risk factor**

Patients with some clinical and genetic characteristics may be more vulnerable to extreme neurotoxicity during platinum drug therapy. Male patients, patients experiencing more severe acute neuropathic symptoms, patients experiencing more severe acute neuropathic symptoms, patients with unusual performance on mid-treatment nerve conduction velocity trials, as well as those who receive higher cumulative oxaliplatin doses, are more likely to experience severe neuropathic symptoms [27]. Furthermore, during oxaliplatin therapy, patients with polymorphisms in the Glutathione S-transferases genes (GSTM1, GSTT1, and GSTP1) are often more prone to develop stage 3-4 collective neuropathy [28]. The use of more than one neurotoxic agent may also increase the risk of developing peripheral neuropathy [29]. Other risk factors, such as body mass index (BMI) and smoking, are less frequently linked to an increased occurrence of peripheral neuropathies [30]. Findings of many researches were inconclusive to clearly determine the risk factors for the final neurological outcome in each patient, for example, several seemingly clear risk factors for peripheral nerve injury have struggled to impress consistent findings in different studies, as the case in patients with diabetes, the age of the patients [31], and patient receiving chemotherapy treatment [30].

**Results and Discussion**

With platinum-based compounds, there are currently no evidence-based pharmacological or supplemental interventions for CIPN prevention. Several drugs have been studied to avoid CIPN, and they have either shown no effect or had an effect in a limited sample study that was not replicated in larger studies (Table 1). In 2011, Kottschade et al. and his colleagues tested the efficacy of vitamin E for preventing peripheral neuropathy induced by chemotherapeutic agent in patients receiving neurotoxic chemotherapy in a double blind, placebo controlled randomized, phase III clinical study enrolling 207 patients receiving either taxanes (n=109), oxaliplatin (n=50), cisplatin (n=8), carboplatin (n=2), or combination chemotherapy (n=20) in which vitamin E was given in 400 mg dose two times daily. The result of this trial demonstrated that the occurrence of grade 2+ sensory neuropathy did not vary between the two arms (34% vitamin E, 29% placebo; \( P=0.43 \)), and there were no significant differences in time to initiation of neuropathy, chemotherapy dosage decreases due to neuropathy, or patient-reported neuropathy symptom between the treatment arms, as shown in table -1. Thus, they found that vitamin E did not seem to minimize the occurrence of sensory neuropathy [32]. Another phase III double-blind, randomized and placebo-controlled study was performed to see whether glutathione could protect patients from developing CIPN as a result of carboplatin/paclitaxel therapy or not [33]. A total of 185 patients were randomly assigned to two groups, the first group received 1.5 g/m² glutathione (n=94) 15 min prior to chemotherapy and the second group receive placebo (n=91). The outcome was not as anticipated, since there were no statistically relevant variations between the two research arms in terms of peripheral neurotoxicity as measured by the EORTC QLQ-CIPN20 and the CTCAE scales (\( P=0.449 \) for grade-2 neurotoxicity, \( P=0.039 \) for time to establish grade-2 neuropathy, in favor of the placebo). The severity of paclitaxel acute pain disorder (\( P=0.30 \) for patients receiving paclitaxel) each 3-4 weeks and \( P=0.002 \), in preference of the placebo, for patients receiving weekly paclitaxel); the period to disease development (\( P=0.63 \)), and obvious toxicities. As such the findings of this study did not encourage the use of glutathione to avoid CIPN caused by paclitaxel/carboplatin [33]. In another large phase III randomized clinical trial, colon cancer patients who were receiving combination therapy of folinic acid, fluorouracil and oxaliplatin (FOLFOX) adjuvant therapy were divided randomly to one of three groups: the first group received 1 g of intravenous calcium glutonate and magnesium sulfate (Ca-Mg) prior and post oxaliplatin therapy, the second group received placebo prior and post oxaliplatin therapy, and the last group received Ca-Mg before and placebo after oxaliplatin therapy [34]. After assessing the patients by the sensory subscale of the EORTC QLQ-CIPN20, an oxaliplatin specific neurotoxicity scale, and the CTCAE 4.0 scale, the finding suggested that Ca-Mg had no impact on total sensory neuropathy. Furthermore, there have been no remarkable variations between research arms in terms of acute neuropathy scores or side effects. In addition, there have been no significant differences in oxaliplatin administered doses of chemotherapy discontinuation rates between arms. As a result, calcium and magnesium infusions were found to be ineffective in preventing oxaliplatin induced peripheral neuropathy. [34].
**Table 1**: Phase II and phase III placebo controlled clinical trial for prevention and treatment of platinum compounds induced peripheral neuropathy

<table>
<thead>
<tr>
<th>Type of the study</th>
<th>Sample size</th>
<th>Patient’s criteria</th>
<th>Assessment tool</th>
<th>Treatment approach</th>
<th>Mechanism of action</th>
<th>finding</th>
<th>Ref.</th>
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<tbody>
<tr>
<td><strong>Prevention</strong></td>
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<tr>
<td>Randomized double-blind placebo-controlled Phase III clinical trial</td>
<td>207</td>
<td>Patients undergoing therapy with neurotoxic chemotherapy</td>
<td>CTCAE version 3.0</td>
<td>Vitamin E (400 mg) BID vs. placebo</td>
<td>Antioxidant</td>
<td>Grade 2 sensory neurotoxicity</td>
<td>Vitamin E: 34% vs. placebo 29%</td>
</tr>
<tr>
<td>Phase III double-blind, randomized and placebo-controlled</td>
<td>185</td>
<td>Patient scheduled to treat with paclitaxel and carboplatin</td>
<td>Sensory subscale of the EORTC QLQ-CIPN20 and CTCAE</td>
<td>Glutathione 1.5 g/m² over 15 min before chemotherapy vs. placebo</td>
<td>Free radical scavenger, decrease the accumulation of platinum in the DRG</td>
<td>no significant differences between the two study arms in term of neurotoxicity CTCAE grade≥2: GSH: 38% vs. placebo: 33%</td>
<td>[33]</td>
</tr>
<tr>
<td>Randomized placebo controlled double blind Phase III trial</td>
<td>353</td>
<td>Patients with colon cancer undergoing adjuvant therapy with FOLFOX</td>
<td>Sensory subscale of the EORTC QLQ-CIPN20 and CTCAE</td>
<td>IV calcium/magnesium Ca-Mg/placebo vs. Ca-Mg/placebo/control group</td>
<td>Cytoprotection by detoxification and ROS scavenging</td>
<td>CTCAE grade≥2 neurotoxicity 43% vs. 46% vs. 45%</td>
<td>[34]</td>
</tr>
<tr>
<td>Randomized Placebo-controlled, double-blinded phase II trial</td>
<td>173</td>
<td>Colon cancer patient receiving FOLFOX adjuvant therapy</td>
<td>CTCAE; Leonard Scale Questionnaire; NCI-Sanofi; cold allodynia test</td>
<td>Calmangafodipir 2-5 µmol/kg by 5 min infusion 10 min prior to oxaliplatin vs. placebo</td>
<td>Protecting cells against oxidative stress by imitating Mg-SOD</td>
<td>Trend toward decreased physician graded neurotoxicity P=0.16 Decreased PRO symptoms P&lt;0.01</td>
<td>[35]</td>
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<tr>
<td>Randomized multicenter controlled trial</td>
<td>355</td>
<td>Patients with breast cancer receiving taxane, platinum, or vinca alkaloid anticaner agent</td>
<td>Patients reported grading of CIPN symptoms</td>
<td>No pharmacological Intervention Exercise during chemotherapy vs. control group</td>
<td>Affects sensory processing in the brain to decrease inflammation</td>
<td>Decreased temperature sensitivity P=0.045 Decreased sensory symptoms P=0.061</td>
<td>[36]</td>
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<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>Double blind, placebo-controlled trial</td>
<td>203</td>
<td>Patients with CIPN</td>
<td>Change in sensory sub scale EORTC-QLQ-CIPN20 score at 4 weeks</td>
<td>Topical amitriptyline, ketamine, with or without Baclofen</td>
<td>Amitriptyline: alters Na channel &amp; Adenosine-AR Ketamine: inhibits NMDA-R, Baclofen: GABA-R agonist</td>
<td>Mean change from baseline of sensory subscale for BAK: 8.1 vs. placebo: 3.8</td>
<td>[37]</td>
</tr>
<tr>
<td>Randomized double-blind placebo-controlled crossover clinical trial</td>
<td>231</td>
<td>Cancer patients with grade 1 sensory pain or with any type of cancer at any stage</td>
<td>BPI-SF average pain scale</td>
<td>Group A Duloxetine 60 mg of taken orally once daily followed by placebo or Group B placebo followed by duloxetine</td>
<td>Inhibitor of the reuptake of serotonin and norepinephrine; sodium channel blocker</td>
<td>Group A an average pain decreased which was more than Group B</td>
<td>[38]</td>
</tr>
</tbody>
</table>

BAK; Baclofen, amitriptyline, ketamine, BID; Twice daily, BPI-SF; Brief pain inventory-short form, CIPN; Chemotherapy Induced Peripheral Neuropathy, CTCAE; Common Terminology Criteria for Adverse Events, DRG; Dorsal root ganglia, EORTC-QLQ; European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ), FACT; Functional Assessment of Cancer Therapy, FOLFOX; Folinic acid, fluorouracil and oxaliplatin, GABA; Gamma aminobutyric acid, GSH; Glutathione, NCI; National Cancer Institute, PRO; Patient-reported outcome measures, R; Receptor, ROS; Reactive Oxygen species.
Calmangafodipir, which is a derivative of mangafodipir magnetic resonance imaging contrast agent, found to resemble the mitochondrial manganese superoxide dismutase enzyme that lowers reactive oxygen species and associated nerve damage following treatment with platinum-based chemotherapeutic agent [35]. After giving such encouraging results in preventing oxaliplatin-induced adverse effects; phase I and phase II trials have been conducted for further assessment of Calmangafodipir activity. Furthermore, another phase II trial was placebo-controlled, double-blinded, in which 173 patients were classified into three groups. The first group (n=60) receive placebo, the second group (n=57) receive 2 mol/kg Calmangafodipir, and the last group (n=45) receive 5 mol/kg Calmangafodipir. The result demonstrated that patients that have been treated with Calmangafodipir had significantly less physician-graded neurotoxicity, far less chilly sensation, and markedly less sensory symptoms on the Leonard scale. These findings suggested that Calmangafodipir tends to avoid oxaliplatin-induced acute and delayed CIPN without affecting tumor outcomes [35]. Exercise for Cancer Patients (EXCAP) was the largest non-pharmacologic treatment trial, in which breast cancer patients who were undergoing chemotherapy based on taxanes, platinum, or vinca alkaloids were randomized to two group: chemotherapy group and chemotherapy plus exercise for cancer patients (EXCAP) group (36). The EXCAP group underwent a six-week progressive walking and resistance exercise program that was systematic, individualized, moderate-intensity, and home-based. In comparison to the monitoring group, exercise decreased CIPN hot and cold symptoms in the hands and feet, as well as numbness and tingling. Patients that were older in age, male, or had breast cancer, experienced more CIPN symptoms reduction by exercise (36). Management techniques include the use of supportive care drugs such as antiepileptics and antidepressants, which are common anti-neuropathic pain medications. Among these medications, duloxetine which stop sodium channel currents, as well as serotonin and norepinephrine carriers disrupt the pain neural network to cause analgesia, is the only treatment that has been linked to a substantial reduction in neuropathic pain in CIPN patients [38,39].

There were no unfavorable side effects associated with the BAK-PLO, and there was no evidence that it was harmful. Therefore, topical BAK-PLO therapy tends to help patients with CIPN symptoms, but further study with higher doses is obligatory in order to have a deeper understanding about the formulation clinical function [37]. Many scientists agree that removing platinum-DNA adducts will be the most beneficial treatment for CIPN patients. Hyperthermia and detoxification are two current methods for improving DNA repair in the presence of DNA adducts. In which, both hyperthermia and detoxification aid the process of cell repair easier by activating the chaperones, causing cellular proteins to refold and re-functionalize resulting in correctly folded proteins, and by removing the platinum compounds from neuronal cells respectively [40]. Furthermore, dose reduction or dose holds are frequently needed to control the combined toxicity of all of these agents, depending on the severity of CIPN.

Conclusion

Among the most common adverse effects of platinum therapy is neuropathy, that might be dependent on the dose or continue and worsen even after treatment discontinuation. The neuropathic pain caused by the CIPN has a significant impact on cancer patients' treatment outcomes. Despite extensive research over the past few decades, peripheral neurotoxicity from platinum-based compounds remains a significant dose-limiting side effect with no proven preventive therapies since platinum compounds tend to harm every aspect of neuronal cells, including expression of genes, mitochondrial homeostasis, the cytoskeleton, cellular organelles, as well as membranes resulting in a variety of symptoms correlated with CIPN disease's severity. As a consequence, treating each of these endpoints separately is extremely difficult. Prompt identification of progressive CIPN symptoms remains the primary pillar of CIPN treatment with the platinum-based agents, since it tends to minimize the severity of symptoms and the likelihood of permanent damage, as well as provide effective preventive and management options.

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Conflicting Interests

The authors declared no conflict of interests.

Data sharing statement

N/A.

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