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REVIEW ARTICLE

Nanotechnology in neurosurgery: a systematic review

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Abstract

Background The application of nanotechnology in medicine encompasses an interdisciplinary field of sciences for the diagnosis, treatment, and monitoring of medical conditions. This study aims to systematically review and summarize the advances of nanotechnology applicable to neurosurgery.

Methods We performed a PubMed advanced search of reports exploring the advances of nanotechnology and nanomedicine relating to diagnosis, treatment, or both, in neurosurgery, for the last decade. The search was performed according to PRISMA guidelines, and the following data were extracted from each paper: title; authors; article type; PMID; DOI; year of publication; in vitro, in vivo model; nanomedical, nanotechnological material; nanofield; neurosurgical field; the application of the system; and main conclusions of the study.

Results A total of 78 original studies were included in this review. The results were organized into the following categories: functional neurosurgery, head trauma, neurodegenerative diseases, neuro-oncology, spinal surgery and peripheral nerves, vascular neurosurgery, and studies that apply to more than one field. A further categorization applied in terms of nanomedical field such as neuroimaging, neuro-nanotechnology, neuroregeneration, theranostics, and neuro-nanotherapy.

Conclusion In reviewing the literature, significant advances in imaging and treatment of central nervous system diseases are underway and are expected to reach clinical practice in the next decade by the application of the rapidly evolving nanotechnology techniques.

Keywords Nanotechnology · Neurosurgery

Introduction

The term nanotechnology refers to the research and development of technology dealing with materials and devices at a matter size scale of less than 100 nm. For a material or a particle to be defined as a nanomaterial or a nanoparticle respectively, they must have at least one of the three outer dimensions smaller than 100 nm. The application of nanotechnology to medicine, referred to as nanomedicine, is an interdisciplinary field of sciences for the diagnosis, treatment, and monitoring of medical conditions [18]. Recent advances in nanomedicine have given a different perspective in the diagnosis and treatment of medical conditions, by intervening at a subcellular level as well as by offering a chance to personalized medical treatment. Even though the central nervous system (CNS) presents many challenges that need to be overcome, nanotechnology and nanomedicine can help neurosurgery make a breakthrough in the forthcoming years. Numerous studies involving nanotechnology, such as targeted drug therapy, theranostics, nanotechnologically advanced materials, molecular imaging, and sutureless anastomosis, have demonstrated the potential of nanomedicine in neurosurgery. This article provides a systematic review of nanotechnological and nanomedical advances applied to the field of neurosurgery.

Materials and methods (Table 1)

The present review was conducted according to the PRISMA statement criteria. The literature search included the material published from January 1, 2009, to August 3, 2019. The

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Table 1 Summary of nanomaterials for each neurosurgical field

Neurosurgical field	Nanomaterial
Vascular neurosurgery	• Liposomes • Polymers • USPIONs • Melanin NPs
Functional neurosurgery	• Carbon monofilament electrodes
Spine surgery and peripheral nerves	• Nanospheres • Nanoscaffolds • Nanopolymers • Hydrogels • Nanofibers
Neuro-oncology	• Liposomes • Nanopolymers • Nanodiamonds • mRNA-NPs • IONPs and SPIONs • Dendrimers • Quantum dots • Gold NPs, nanorods, nanoshells • Hydrogels • Magnetic NPs • Graphene oxide • Nanoscaffolds • Nanocrystals
Neurodegenerative diseases	• Magnetic NPs • Gold NPs • Liposomes • Nanofibers • Nanopolymers • Single-wall carbon nanotubes • Graphene quantum dots • Nanosheets
Head trauma	• Lab-on-a-chip

search was open to both in vitro and in vivo studies. Inclusion criteria included nanomedical or nanotechnological advances applicable to neurosurgery. The review included only original papers published in PubMed-indexed peer-reviewed journals, clearly stating nanomedicine and nanotechnology in neurosurgery, the experimental models, and the radiological techniques applied. Exclusion criteria included as follows: papers not describing original research (i.e., reviews, perspectives, letters to the editor, commentaries, and abstracts), non-English language papers, description of new chemical or physical properties of nanomedical molecules or nanotechnological systems or biological models or without application to a neurosurgical field, and papers focusing on nanotechnology but not primarily on neurosurgery.

The search was performed using the Boolean logic of the advanced search of the PubMed database and by scanning reference lists of the resulting articles. The search terms were (((((((nanomedicine) OR nanotechnology) OR liposome) OR dendrimer) OR quantum) OR gold) OR niosome) AND neurosurgery. Eligibility assessment was performed independently in an unblinded standardized manner by two reviewers. Disagreements between reviewers were resolved by consensus. The following data were extracted from each paper: title, authors, article type, PMID, DOI, year of publication, in vitro/in vivo model, nanomedical/nanotechnological material, nanofield, neurosurgical field, the application of the system, and main conclusions of the study. Unfortunately, a quantitative comparison between studies or groups was not possible because of the heterogeneity of the biological models and technical discrepancies between different nanomedical/nanotechnological systems. Therefore, no statistical analysis was performed.

Results

The PubMed search yielded 1984 items. Among the collected studies, 1794 were discarded because they met the exclusion criteria. Full texts of 190 articles were retrieved and were further investigated. A total of 78 original studies were included in our review. The selection of the studies was performed according to PRISMA guidelines and the process is presented as a flow diagram (Fig. 1). In detail, the articles excluded according to type classification as given by PubMed are as follows: reviews (358), case reports (173), clinical studies (93), clinical trial (71), Clinical Trial Protocol (3), Clinical Trial Phase I (3), Clinical Trial Phase II (2), Clinical Trial Phase III (2), Controlled Clinical Trial (52), meta-analysis (32), multicenter studies (34), observational studies (19), randomized controlled trial (50), research support N.I.H. Extramural (131), research support N.I.H. Intramural (4), Systematic Reviews (41), research support US Government (167), research support US Government PHS (167), research support US Government Non-PHS (32), research support Non-US Government (453), and other types of articles (97). Eight (8) citations [6, 13, 19, 25, 32, 57, 69] were added after reviewing the bibliographies of the included papers. A categorization of the studies according to nanofield and neurosurgical field is reported in Figs. 2 and 3. An analysis of the type of articles included and excluded in our study is presented in Figs. 4 and 5. We found eight studies pertaining to neuroimaging, ten studies pertaining to neuro-nanotechnology, and four pertaining to neuroregeneration, thirteen were about theranostics, and finally the majority of studies (a total of 43) were about neuro-nanotherapy. The distribution of the studies in fields of neurosurgery was as follows: one in functional neurosurgery, one in head trauma, twelve in neurodegenerative diseases, forty-seven in neuro-oncology, nine in spinal surgery and peripheral nerves, six in vascular neurosurgery and two studies could apply to more than one field (neuro-oncology and neurodegenerative diseases). The distribution of the studies through time is presented in Fig. 6. Nineteen of the articles are in vitro experiments, whereas forty-seven are in vivo studies and the remaining twelve studies contain both in vitro and in vivo parts. Only four studies were conducted with human subjects [10, 13, 19, 20] and the rest included studies on animals, such as mice, rats, sheep, and canines.

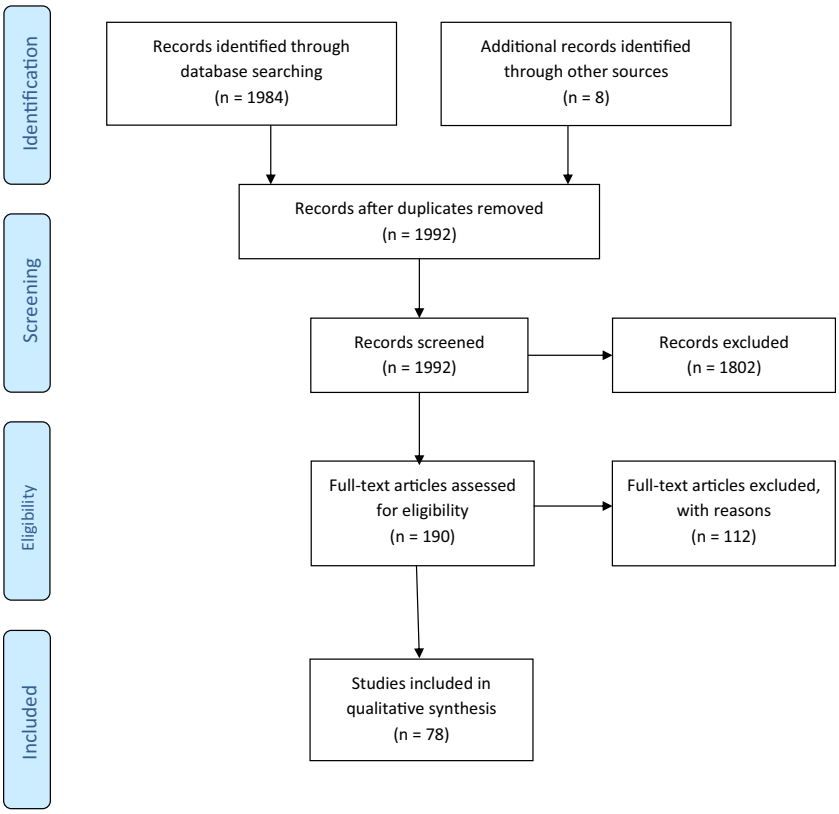

Fig. 1 Flow diagram of selection according to PRISMA guidelines

Discussion

We will discuss nanotechnology development in different aspects of neurosurgery.

Traumatic brain injury

Traumatic brain injury (TBI) represents a critical health problem worldwide, affecting nearly 10 million people annually. Its clinical manifestations come from the damage to neuronal axons during the injury. The neuronal axon can be stretched, sheared, or intersected, which will eventually lead to axonal swelling, increased cytoplasmic permeability, consecutively to calcium influx, and finally to neuronal death [49].

Medical and surgical managements of TBI have seen significant advances in the last decade. Currently there is emerging nanotechnology research in two fields:

a. Identification of biomarkers at a micro- or nanomolecular scale either in blood or in CSF that reflects the loss of

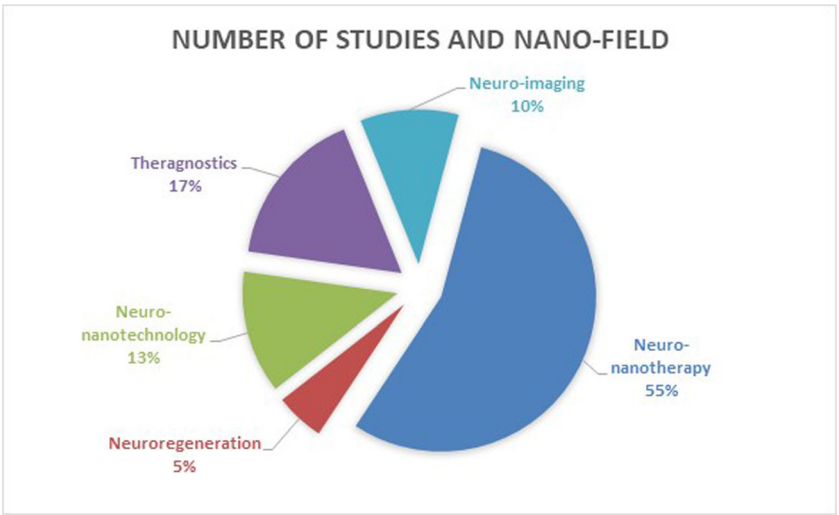

Fig. 2 Analysis on the number of studies according to nanofield

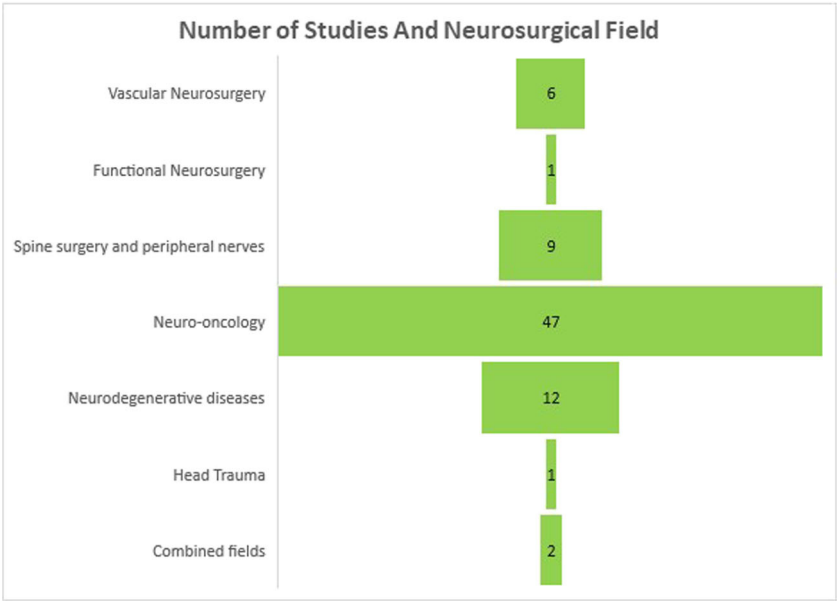

Fig. 3 Analysis on the number of studies according to neurosurgical field

neuronal integrity, altered brain protein metabolism, and altered synaptogenesis. Strongly predictive biomarkers of functional outcome in a mild TBI patient are myelin basic protein (MBP) and myelin-associated glycoprotein (MAG). These proteins are known products of both acute and chronic oligodendrocyte demyelination and are currently the subject of research, employing microwave and magnetic (M2) proteomics for their level estimation [14].

b. The development of a micro-chip designed to nanomagnetically isolate brain-derived extracellular vesicles. Using RNA sequencing and machine learning processing, the micro-chip can detect the extracellular vesicle micro-RNA (miRNA) load, which is correlated to the state of TBI. It has a claimed accuracy of 99% in identifying the signature of injured versus control mice, where the injured group consisted of a heterogeneous population. Furthermore, in the same study, the intensity of the injury as well as the elapsed time since injury and the presence of a history of brain injury were also successfully predicted [30].

Neurodegenerative diseases

Neurodegenerative diseases continue to present a significant challenge, as despite intensive research, currently there is no effective treatment for them. Current therapies focus on treating the symptoms but do not stop the progression of the disease, which eventually leads to severe disability. Finding a treatment that can affect the course of the disease will have a significant impact on survival and quality of life. Nanomedicine and nanotechnology could potentially offer solutions to the treatment of Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD).

The most common cause of dementia is Alzheimer's disease (AD), which is affecting approximately 40–50 million

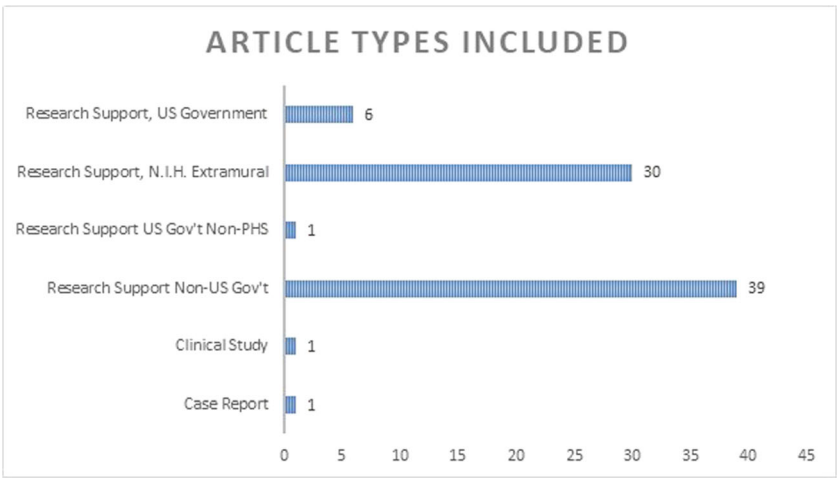

Fig. 4 The number of articles included

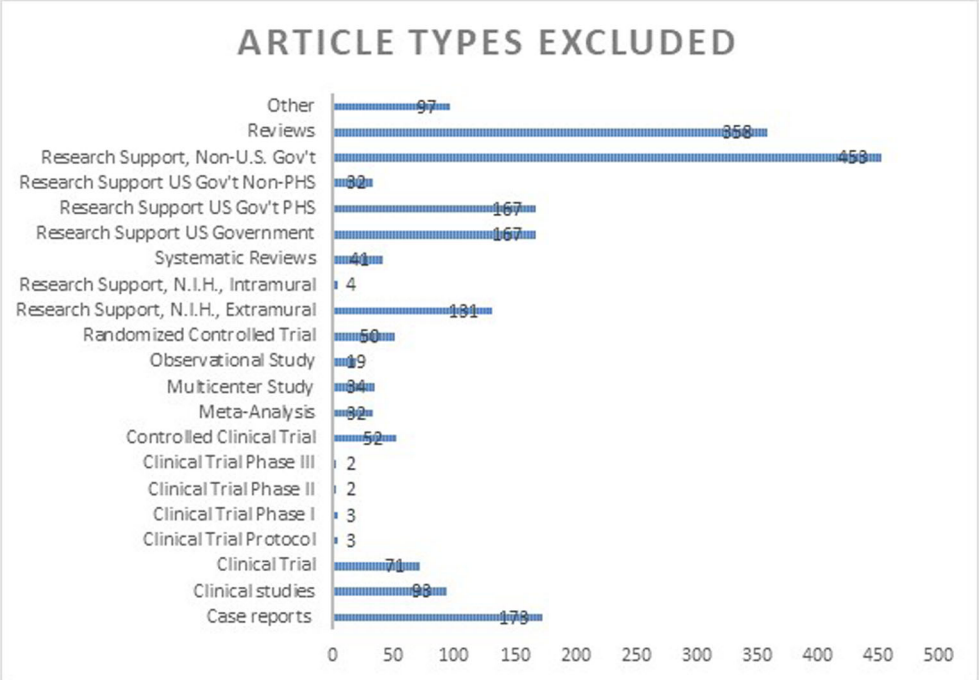

Fig. 5 The number of articles excluded

people worldwide aged over 50 years and is the commonest chronic neurodegenerative disorder. The cardinal pathological feature of AD is the formulation of amyloid plaques due to the aggregation of the amyloid-b (Ab) peptide. Consequently, intraneuronal neurofibrillary tangles develop in specific regions and are composed of hyperphosphorylated forms of the microtubule-associated protein, tau [23]. Furthermore, the brain develops significant neuronal loss and neuroinflammation [22]. New criteria that incorporate biomarkers have been established in order to identify AD at its early stages, and subsequently fight the progression of the disease by applying a strategy with disease-modifying drugs (e.g., lithium, rosiglitazone, tarenflurbil), psychotropic agents, and psychosocial interventions [50]. Nanomedicine has offered a lot in the treatment of AD. Newer drugs have been developed, and old ones have been improved with the help of nanocarriers, increasing the bioavailability of the drug and enhancing the levels of the active pharmaceutical agent [2]. Furthermore, nanomedicine has been targeting Aβ amyloid, by deploying strategies that can affect either the formulation of the amyloid or its breakdown [39]. Modern treatment strategies include promising and quite popular gene therapy [33] and combined modalities. The latter refers to the use of ultrasound or MRI in order to temporarily open the blood-brain barrier (BBB) and either increase the bioavailability in the brain of the nanodrug or the conventional drug or promote a

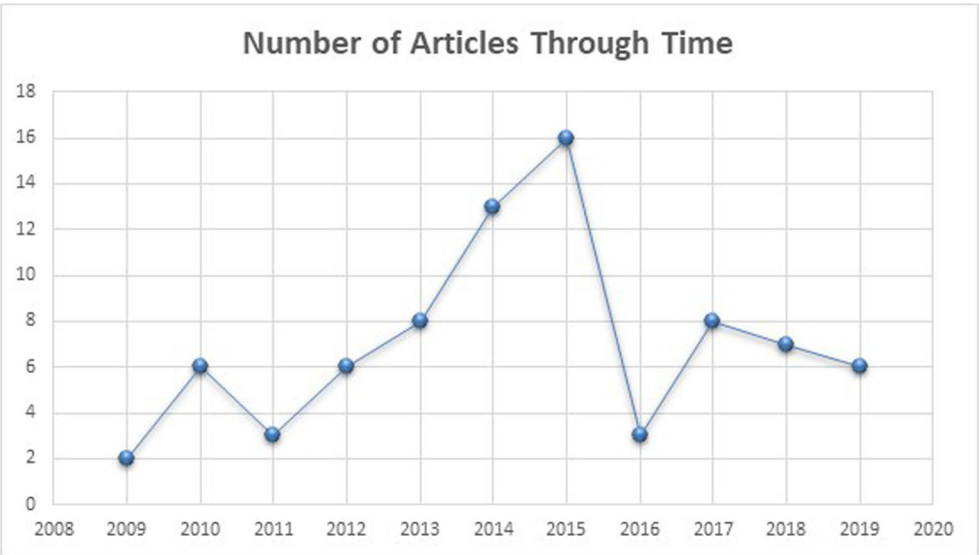

Fig. 6 Distribution of articles through time

drug which could not otherwise cross the BBB. Finally, nanotechnological advances, such as biosensors with nanosheets, have also been very promising in diagnosing AD in its early stages [70].

Parkinson's disease (PD) is the second most common chronic, progressive neurodegenerative disorder. The prevalence of the disorder is 1–2 per 1000 in the general population, whereas in people over the age of 60 years, it is 1% [58]. The clinical manifestations of PD include the classic triad of resting tremor, bradykinesia, and muscle rigidity, while also common symptoms are impaired postural reflexes and varying degrees of autonomic dysfunction. The most distinct pathologic characteristic is the degeneration of dopaminergic neurons which lie in the substantia nigra pars compacta and the presence of intracytoplasmic inclusions (a.k.a. Lewy bodies) in these neurons. Many neurotransmitters are involved in direct, indirect, and hyperdirect pathways in the basal ganglia circuits, which translates to the use of several drugs daily in order to improve different aspects of the PD symptomatology such as motor, emotional, cognitive symptoms, and/or psychiatric complications. The most prominent medication in the treatment of PD is levodopa, but other medications such as monoamine oxidase type B inhibitors (MAOBIs), amantadine, anticholinergics, beta-blockers, and dopamine agonists can be an option in order to avoid levodopa-related complications. Most of the long-term side effects of levodopa are related to its brief activity, which corresponds to a pulsatile mode of stimulation of dopamine receptors, instead of continuous stimulation, which is present in the normal nigrostriatal pathway. Even though there are many drug delivery systems, including infusion pumps and skin patches, in order to provide a more continuous stimulation resembling the normal physiology of dopamine receptors, the desired effect has not yet been established [28]. Nanomedicine has offered newer drug delivery systems that can increase the bioavailability of existing drugs but can also be used in the delivery of newer treatments such as gene therapy [2]. Furthermore, most popular are the combined therapies as described above in AD, which include an ultrasound or MR stimulus in order to temporarily disrupt BBB and allow the passing of several drugs [33]. Nanotechnology has also offered very promising results in detecting PD with the help of biosensors based on gold nanoparticles, quantum dots, or carbon nanotubes [26, 29, 56]. Besides pharmacological advances in the treatment of PD, nanotechnology has developed newer carbon monofilament electrodes that can produce even better results in electrophysiology study during deep brain stimulation [9].

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease, caused by an abnormal expansion of CAG repeats within the Huntingtin (HTT) gene. Most common pathologic signs of the disease are the extensive neuronal degeneration in the neocortex and the neostriatum, which leads to the main clinical manifestations of the disorder such as bradykinesia, cognitive decline, psychiatric disorders, and the hallmark, progressive involuntary choreic movements [43]. Nanomedicine has offered better nanodelivery systems for gene therapy [2]. Promising results also yielded by combining treatment strategies, i.e., focused ultrasound, in order to enhance vascular permeability and open BBB for delivering liposomes carrying plasmids for gene therapy of HD [35]. Moreover, nanomedical advances also contribute to the construction of better research mechanistic models in order to investigate the molecular pathophysiology of neurodegenerative movement disorders such as HD, giving as well insights of their clinical manifestations [25].

CNS tumors

Tumors of the CNS remain a significant challenge in neurosurgery. Recent research has turned to nanotechnology and nanomedicine for modern therapeutics and innovative nanobiological and nanotechnological platforms. Therefore, any nanoparticle that can be developed, such as liposomes, polymeric nanoparticles, dendrimers, quantum dots, supermagnetic nanoparticles, carbon nanomaterials, gene therapy, and immunotherapy delivered by nanosystems, has been tested against a brain tumor. Many existing anticancerous medication have been enhanced by nanotechnology, in a way that diminishes the adverse effects of the active drug and improves both the bioavailability and the efficacy. In a phase 1 trial to assess safety and pharmacokinetics, 34 patients received intravenous administration of liposomal irinotecan and did not show any signs of toxicity [10]. Nanodiamonds have been used to enhance the effect of doxorubicin. The nanosystem of doxorubicin has been studied in a preclinical glioma model administrated with the convection-enhanced delivery method and demonstrated quite promising efficacy [63]. Doxorubicin has also been conjugated with polyethylene glycol (PEG) and a biodegradable, non-toxic, non-immunogenic platform, PMLA [poly (b-L-malic acid)]. This nanosystem has successfully demonstrated its efficacy in in vitro glioma cell lines but even in several breast carcinoma cell lines [47]. Liposomes and polymeric nanoparticles have served well drug delivery in neuro-oncology offering new perspectives and providing with promising results with a variety of chemotherapeutic agents such cisplatin, oxaliplatin, paclitaxel, and temozolomide [7, 34]. However, nanodrug delivery systems have also been used for delivering gene therapy. Polymeric nanoparticles showed good efficacy in transporting non-viral gene therapy [40], while intranasal administration of plasmid DNA nanoparticles resulted in long-term gene changes in the rat brain [2].

Nanotechnology has also been deep in neuro-immunology using the immune system and its components [52] in order either to deliver inhibitors [41] or to apply immunotherapeutic treatments [53]. Encapsulated lipid nanoparticles aim at

untargeted tumor RNA in an effort to activate an immune response in favor of the patient [51], while liposomes with GGTase I (geranylgeranyltransferase I) demonstrated inhibition of diacylglycerol kinase alpha for the treatment of resistant mesenchymal glioblastoma brain cancer phenotype [46]. Other nanomedical advances include the use of dendrimers as a carrier system for epidermal growth factor. Their intratumoral or intracerebral administration showed enhanced efficacy in comparison to the administration of non-nanoconjugated epidermal growth factor [64]. Another promising nanocarrier system is magnetic nanoparticles. Iron oxide nanoparticles conjugated to monoclonal antibodies not only demonstrated an antitumor effect [27] but also can enhance radiosensitivity of the glioblastoma [5]. Quantum dots and gold nanoparticles are particularly preferable in the research for brain cancer treatment. The main reason for this is their ability to be used as both neuroimaging and neurotherapeutic means. This gave birth to a new concept that of theranostics. The idea of simultaneously imaging and treating the tumor is gaining much more attention in the last decade. Semiconductor quantum dots have been used to label and modulate microglia and at the same type act as a carrier system for a tumoricidal drug [42]. The synthesis of near-infrared quantum dots presents with good physicochemical characteristics that are used both to depict gliomas and to apply photodynamic therapy [38]. Furthermore, quantum dots have modified in that way to be able not only to easily cross the BBB but also to fluorescence glioma and its tumoral vasculature [24]. Carbon nanodots with high water solubility have also been modified in order to enter glioma cells and fluorescence in vivo gliomas [62]. Oxide nanoparticles have been also optimized to therapeutically target specifically gliomas, and it was demonstrated that it could increase the cellular uptake of the carried drug in in vitro studies [60] and also increase animal survival in several studies [21, 61]. Iron particles have also been used in combined treatment strategies for gliomas. More specifically, magnetic iron nanoparticles have been injected in tumor-bearing rats and afterwards an exogenous magnetic field has been applied in order to cause hyperthermia of the tumor [65]. Superparamagnetic iron oxide nanoparticles have been used as a delivery system for immunogenic peptides and stimulants of the neural system contributing in this way to the immune system's response to cancer [54]. Finally, ultra-small gadolinium oxide nanoparticles have been shown to have great potential in the visualization of glioma cells [15]. Gold nanoparticles are the spearhead of nanotechnology because they offer a great variety of applications and they have been extensively used in the treatment of gliomas. Gold nanorods have been delivered inside the tumor with neural stem cell–mediated delivery, and combined with photothermal therapy, they have decreased the recurrence rates not only for gliomas but also for breast cancer as well [45]. Gold nanoparticles have also been conjugated to know chemotherapeutic agents such as cisplatin. The administration of this nanosystem has been combined to an MR-guided focused ultrasound to intensify glioblastoma treatment, which achieved great results in the growth reduction of GBM tumors [11]. Moreover, gold nanoparticles have been combined with immunotherapy. Gold nanoshell–loaded macrophages have been used in hyperthermia treatment applications, and they demonstrated the potential of monocytes to be used as nanoparticle vectors for light-based cancer therapies [8]. BBB disruption–based therapies are another nanotechnological idea that uses magnetic fields and/or ultrasound to temporarily disrupt BBB and thus allow the passage of a nanodrug [12, 66]. Despite the rapid development of theranostics, neuroimaging has also evolved and offers promising results in imaging brain tumors. This can help in diagnosis and follow-up and even in the surgical excision of the tumor. In this category, 5-aminolevulenic acid is used perioperatively to fluorescence the tumor and to improve the resection of the tumor [59]. A nanotechnological advance, the hand-held Raman scanner, could accurately detect gold-silica surface-enhanced Raman scattering nanoparticles that are embedded in glioblastoma and thus guide a complete resection [48]. Other nanotechnological advances include nanoscaffolds and magnetic carriers, such as magnetic liposomes, that can demonstrate high specificity and efficacy in tumor growth [67, 69]. Transferrin-modified nanoscaled graphene oxide doxorubicin exhibited a significantly improved effect on tumor growth [37], as well did a thermosensitive liposome which demonstrated even better results than the conventional liposomes [31]. Last but not least, liposomes have also been used in the treatment of tumor-like pathologies of the brain, such as abscess, reducing the toxicity of an intraventricular or intrathecal delivery and enhancing the effect of the active drug [20].

Spine and peripheral nerve pathologies

Spine surgery is an evolving field in technological advances. Newer applications in spinal fusion, drug delivery, neuronal and disk regeneration, prophylaxis for spinal infection, and molecular imaging are just a sample of areas that modern bioengineering and medicine can offer to neurosurgery. Nanotechnology has offered a lot in spinal fusion by engineering new materials with extraordinary physicochemical properties. Nano-roughened surface modifications of existing titanium interbody implants have been reported to promote the differentiation of stem cells into osteoblast lineage with better results than the widely used and well-established polyetheretherketone (PEEK) cages [19]. A newer bioabsorbable, self-retaining fusion cage has been developed and can offer better results in terms of stability and fusion in comparison again with PEEK [6]. In addition to cages, gel scaffolds of bone morphogenetic protein-2 (BMP-2)–binding peptide amphiphile nanofibers are reported to promote

osteogenesis and achieve both endogenous and exogenous fusion [32]. Another area of spine surgery, spine trauma, received a lot of attention and research. Nanotechnology has developed better materials that can be used for filling fractured vertebrae instead of traditional cement. Electrospun nanofibrous poly(D,L-lactide-co-e-caprolactone) balloons have been manufactured and tested for filling a compressed fractured vertebra, and present with the advantages of calcium phosphate cement but without disadvantages [57]. Regenerative medicine is a promising multidisciplinary field of research that encompasses translational research, tissue engineering, and molecular biology. Nanotechnology has found a place in that field and offer very promising therapies to spine surgery and peripheral nerves. Composite hydrogels of drug-loaded poly(lactide-co-glycolide) (PLGA) nanoparticles are being investigated for their potential intrathecal administration in spinal cord injuries. Nanotechnology has also developed scaffolds and nanofiber nets that are used to promote functional recovery and nerve regeneration. For example, linear-ordered collagen scaffold fibers with collagen-binding brain-derived neurotrophic factor have been implanted in a complete transection of the spinal cord in canine and demonstrated a quite promising therapeutic effect in spinal cord injury. Nanofibrous membranes produced by the electrospinning process were used to assess the cicatrization process and prevent excessive scar formation, with good results [3].

Nanotechnology offers promising results in nerve regeneration, bridging the neural gap over 2 cm, which is approximately the threshold for neurorrhaphy. Thus, highly aligned nanocomposite scaffolds produced by electrospinning and electrospraying have demonstrated great potential in promoting and guiding neuronal regeneration and tissue growth [68]. Other approaches in neural regeneration include an immunomodulatory approach. A CX3CR1 ligand has been used to stimulate nerve repair in a nerve-guidance scaffold. The study suggested that the infiltrating immune cellular milieu after nerve injury propagates regeneration and creates a favorable environment for repair [44].

Neurovascular disorders

In the field of neurovascular disorders, nanotechnology is offering promising advances mainly in the management of stroke and the imaging of vascular malformations. Stroke is classified into ischemic stroke and hemorrhagic. Ischemic stroke is the fifth leading cause of mortality and morbidity in the modern world [16, 17]. Ischemic strokes account for approximately 87% of all strokes and nearly 1 out of 4 people have had a history of a previous stroke [4]. The hemorrhagic stroke represents 10–15% of all strokes, and it is linked with a higher mortality risk than the ischemic stroke.

Advances in research in the last 10 years focus on the development of newer therapeutic agents for neuroprotection. Many nanosystems based on liposomes have incorporated a variety of molecules such as melanin, VEGF with transferrin, and even hemoglobin in order to provide a neuroprotective effect on the ischemic brain. Their effect is possible through not only scavenging excessive reactive oxygen and nitrogen species (RONS) but also promoting vascular regeneration and microvascular perfusion [36, 55]. Pertaining to therapy strategies, nanomedicine has developed new masking techniques from the human body immune system offering thus existing drugs such as tPA, with greater bioavailability, less systemic adverse effects, and better targeting [1].

In the field of neuroimaging, nanomedicine has helped a lot with the introduction of quantum dots and nanoparticles such as ultra-small superparamagnetic iron oxide nanoparticles. These agents can be used as a macrophage imaging agent resulting in the visualization of inflammatory cells and thus identifying endothelial damage for early detection of aneurysms or any other intracranial vascular malformation with a high probability of rupture [13]. These achievements could help in the future even in identifying vascular distributions predisposed to vasospasm or in distinguishing penumbra from the infarcted area.

Conclusion

It is expected that in the near future nanotechnology will have a significant impact in the diagnosis and treatment of many diseases of the central nervous system. The continue evolution of technology will offer new opportunities which will revolutionize imaging and treatment modalities.

Compliance with ethical standards

For this type of study, formal consent is not required. This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest

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