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REVIEW PAPER

Bone Marrow-Derived Mononuclear Cells in the Treatment of Neurological Diseases: Knowns and Unknowns

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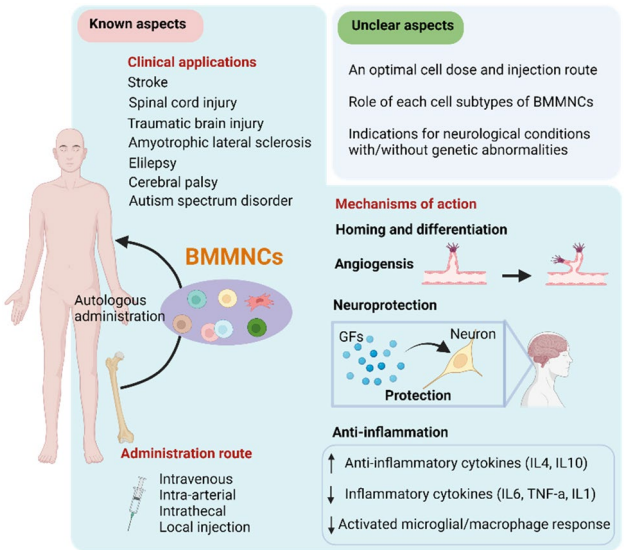
Abstract

Bone marrow-derived mononuclear cells (BMMNCs) have been used for decades in preclinical and clinical studies to treat various neurological diseases. However, there is still a knowledge gap in the understanding of the underlying mechanisms of BMMNCs in the treatment of neurological diseases. In addition, prerequisite factors for the efficacy of BMMNC administration, such as the optimal route, dose, and number of administrations, remain unclear. In this review, we discuss known and unknown aspects of BMMNCs, including the cell harvesting, administration route and dose; mechanisms of action; and their applications in neurological diseases, including stroke, cerebral palsy, spinal cord injury, traumatic brain injury, amyotrophic lateral sclerosis, autism spectrum disorder, and epilepsy. Furthermore, recommendations on indications for BMMNC administration and the advantages and limitations of BMMNC applications for neurological diseases are discussed.

Graphical Abstract

BMMNCs in the treatment of neurological diseases. BMMNCs have been applied in several neurological diseases. Proposed mechanisms for the action of BMMNCs include homing, differentiation and paracrine effects (angiogenesis, neuroprotection, and anti-inflammation). Further studies should be performed to determine the optimal cell dose and administration route, the roles of BMMNC subtypes, and the indications for the use of BMMNCs in neurological conditions with and without genetic abnormalities.



Keywords Bone marrow-derived mononuclear cells · Administration route · Mechanism of action · Neurological diseases · Cell therapy

Extended author information available on the last page of the article

Background

Neurological diseases encompass acute neurological injuries, cerebrovascular accidents, chronic neurodegenerative diseases, and neuroinflammatory diseases, and their manifestations lead to significant social and economic burden (Hess and Borlongan 2008). Traditionally, the treatment of these diseases consists mainly of neurorehabilitation; however, neurorehabilitation provides only modest symptomatic relief in severe cases. Despite continuous and extensive efforts, treatment options for patients with neurological diseases are still limited (Tamburin et al. 2019).

Recently, cell therapy has emerged as a promising approach for treating neurological disorders due to its self-renewal and replacement capacities, paracrine effects, and/or immunomodulatory ability. Neural stem cells (NSCs) have been continuously explored as a form of cell replacement therapy for neurological disorders. NSCs have shown beneficial effects in replacing injured components of the nervous system. However, the administration of NSCs into the brain is associated with several issues, including safety and ethical issues and scientific and regulatory obstacles (Mathews et al. 2008). Additionally, the long-term culture of NSCs in vitro could result in gene expression changes, reducing the neurogenic potential of NSC therapy (Anderson et al. 2007). Thus, an alternative cell therapy mitigating pathology not only through neural replacement but also through neurotrophic effects has become an attractive potential approach for the treatment of neurological diseases.

Bone marrow–derived mononuclear cells (BMMNCs) are a heterogeneous group of cells, including progenitor cells, such as hematopoietic stem cells (HSCs); mesenchymal stromal/stem cells (MSCs); endothelial progenitor cells (EPCs); very small embryonic-like cells; and immune cells, such as monocytes, T cells, B cells, and natural killer cells (Vahidy et al. 2016; Suda 2017). BMMNCs can be easily isolated from bone marrow (BM) aspirate by density gradient centrifugation. Due to their ease of processing, with no need for extensive preparation or cultivation, BMMNCs have become an attractive option for cell therapy in regenerative medicine. To date, BMMNCs have been evaluated in many clinical studies for the treatment of various neurological diseases (Sharma et al. 2020b, c, f; Thanh et al. 2019; Costa-Ferro et al. 2020; Nguyen Thanh et al. 2021; Taguchi et al. 2015b). However, their mechanisms of action contributing to treatment outcomes remain elusive. Furthermore, the optimal number of cells, route of administration, and number of doses of cells are unclear; therefore, further investigation is needed.

The aim of this overview is to analyze the knowns and unknowns in the use of BMMNCs for cell therapy, including their subtypes; their optimal administration route; their mechanisms of action; and their applications in neurological diseases, including stroke, cerebral palsy (CP), spinal cord injury (SCI), traumatic brain injury (TBI), amyotrophic lateral sclerosis (ALS), autism spectrum disorder (ASD), and epilepsy. In addition, we discuss recommendations on indications for BMMNC administration as well as the advantages and current limitations of BMMNCs in the treatment of these diseases.

Clinical Applications of BMMNCs in the Treatment of Neurological Diseases

BMMNCs in the Treatment of Stroke

Stroke, which can be subdivided into ischemic and hemorrhagic types, is a medical emergency in which there is an interruption in blood flow to the brain. Ischemic stroke is the predominant type, accounting for 87% of all strokes (CDC 2022). Despite reduced mortality due to advances in treatment, the proportion of stroke patients with severe neurological sequelae remains high. In addition to standard treatments, BMMNC administration has recently become an alternative option for treating stroke.

BMMNCs have been used to treat stroke at different phases, including the acute, subacute, and chronic phases, in 14 clinical trials with a total of 224 patients (Table 1). In those studies, the BMMNCs were mainly injected through either the intra-arterial route or the intravenous route, with only a few studies performing intracerebral or intrathecal infusion. The number of cells administered ranged from 10 to 500×10^6 cells, or, where a cell dose was specified instead, the dose ranged from 1 to 10×10^6 cells/kg of body weight (Table 1). These studies reported no adverse events or serious adverse events, indicating that the administration of BMMNCs appears to be safe in patients with stroke (Table 1).

However, the efficacy of BMMNC therapy remains unclear. Suarez-Monteagudo et al. reported some positive changes in neuropsychological evaluation results, such as improved blood flow in the patient's brain and slight changes in neuronal activity, after intracerebral injection of BMMNCs (Suarez-Monteagudo et al. 2009). In a retrospective cohort study, intravenous administration of BMMNCs improved neurological outcomes and enhanced cerebral blood flow and metabolism compared with standard traditional stroke treatments (Taguchi et al. 2015b). Improvements in the Barthel Index (BI) 7-scale (Battistella et al. 2011; Savitz et al. 2011; Bhasin et al. 2012; Prasad et al. 2012), National Institutes of Health Stroke Scale (NIHSS) (Battistella et al. 2011; Savitz et al. 2011; Friedrich et al. 2012; Prasad et al. 2012; Rosado-de-Castro et al. 2013b; Taguchi et al. 2015b), and modified Rankin Scale (mRS)

Table 1 Clinical applications of BMMNCs in the treatment of stroke

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
1	Suarez-Monteagudo et al. (2009)	An open-label study	120–150 ml	5 ± 0.95 years poststroke	Intracerebral	$39.1 \pm 14.2 \times 10^6$, 92.1 ± 1.6% viability	6.3 ± 2.1% $CD34^+$	5	Headache (disappeared within 48 h), drowsiness, nausea, high blood pressure, fever, and hyperglycemia (disappeared within 24 h)	Improvement in neurological outcomes, including motor defects, equilibrium, locomotion, neurological condition, and neurophysiological outcomes
2	Battistella et al. (2011)	An unblinded, uncontrolled phase I study	80 ml	69.17 ± 3.4 days poststroke	Intra-arterial	$1–5 \times 10^8$, > 93% viability	NA	6	No complications or adverse events during 180-day follow-up	Reduction in NIHSS score (100%) and mRS score (83%), increase in BI score (83%) posttreatment
3	Savitz et al. (2011)	An open-label study with no control group	2 ml/kg of body weight	Average of 20 (8 to 53) hours after symptom onset	Intravenous	Different doses: 7×10^6/kg, 8.5×10^6/kg, and 10×10^6/kg, 95.7 ± 1.1% viability	3 ± 1.3% $CD34^+$ 2.2 ± 1% Lin^-CD34^+, 1.3 ± 0.7% $Lin^-CD34^+CD133^+$, 0.02 ± 0.01% $Lin^-CD34^+CD133^+$, 20.2 ± 5.1% T cells, 6.1 ± 1.2% B cells, 4.4 ± 2.6% NK cells	10	2 patients had transiently increased transaminase levels. No seizures or cerebral infarcts	Reduction in NIHSS score and mRS score, increase in BI score posttreatment
4	Bhasin et al. (2012)	A nonrandomized controlled clinical trial	40–50 ml	9.17 ± 1.03 days poststroke	Intravenous	$54.6 \pm 2.5 \times 10^6$	0.31 ± 0.26% $CD34^+$	12	No major/moderate adverse events observed	Increase in mBI and Fugl–Meyer Assessment scores, Ashworth tone and number of cluster activations of Brodmann areas

Table 1 (continued)

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
5	Prasad et al. (2012)	A nonrandomized phase I clinical study	114.4 ± 29.8 (60–160 ml)	14.36 ± 2.66 days after onset of stroke	Intravenous	$85.6 \pm 50.5 \times 10^6$ ($19.44–185.75 \times 10^6$) 3% viability	1.18 ± 1.1% (0.08–3.34%) $CD34^+$	11	No serious adverse events were observed during the study	Favorable outcomes were found in 7 of 11 (64%) as per scale scores: BI 7 of 11 (64%), NIHSS 5 of 10 (50%) and mRS 6 of 11 (54.5%) patients
6	Friedrich et al. (2012)	A nonrandomized, uncontrolled trial	50 ml	6 ± 1.8 days (range 3–10) after onset of stroke	Intra-arterial	Mean: 22.08×10^7 cells (range 5.1×10^7-60×10^7), > 90% viability	NA	20	No serious adverse events related to cell infusion	Reduction in NIHSS score
7	Moniche et al. (2012)	A single-blind (outcome assessor) controlled phase I/II trial	50 ml	6 ± 1.3 days after onset of stroke	Intra-arterial	Mean: 1.59×10^8, 93% viability	3.38×10^6 CD34 +	10	No death, stroke recurrence, or tumor formation during follow-up	Increase in β-NGF levels, No significant differences in neurological function at 180 days
8	Rosado-de-Castro et al. (2013b)	A nonrandomized, open-label phase I clinical trial	80 ml	55.18 ± 7.62 days after onset of stroke	Intra-arterial and intravenous	$1–5 \times 10^8$	0.56–2.48% HSCs, 0.01–0.04% MSCs, 0.01–0.02% EPCs	12	No deaths or recurrence of stroke 2 patients in the intra-arterial group; 5 patients in the intravenous group had seizures	Reduction in NIHSS in iv group The intra-arterial route led to greater uptake in the liver and spleen and lower uptake in the lungs at 2 h than the intravenous route

Table 1 (continued)

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
9	Prasad et al. (2014)	A phase II, randomized, multicenter, open-label, parallel-group trial with blinded end point assessment	108.9 ± 33.9 ml	Median time of 18.5 days after onset (7 days ≤ time interval < 30 days)	Intravenous	$280.75 \times 10^6 \pm 162.9$, 93.2% viability	$2.9 \pm 2.8 \times 10^6$ $CD34^+$	58	Adverse events were similar between untreated and treated groups	No significant difference in NIHSS, BI, or mRS scores, change in infarct volume between untreated and treated groups
10	Sharma et al. (2014)	A nonrandomized trial	120 ml	Averaged 40.54 months poststroke (4–144 months)	Intrathecal	1×10^6 cells/kg of body weight, 96% viability	NA	24	None of the patients had any major adverse events	Out of 24 patients, 12 improved in ambulation, 10 in hand function, 6 in standing balance, 9 in walking balance, and 10 in functional status
11	Moniche et al. (2014)	A single-blind controlled phase I/II trial	50 ml	Between 5 and 9 days post-stroke	Intra-arterial	$1.59 \times 10^8 \pm 1.21 \times 10^8$/$2.17 \times 10^6$/kg of body weight	$3.38 \times 10^6 \pm 2.33 \times 10^6$/47,363/kg $CD34^+$	10	No adverse events reported	Decrease in MMP-2 level No difference in MMP-9, GM-CSF, or PDGF-BB between BMMNC-treated patients and controls
12	Taguchi et al. (2015a)	A nonrandomized open-label study design	25 ml and 50 ml	7–10 days post-stroke	Intravenous	$2.9 \pm 1.0 \times 10^8$	$4.4 \pm 2.3 \times 10^6$ $CD34^+$	11	No apparent adverse effects were observed	Reduction in NIHSS score, increase in favorable outcomes and BI score

Table 1 (continued)

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
13	Bhasin et al. (2016)	A randomized placebo-controlled clinical trial	40–50 ml	9.7 ± 0.84 months poststroke	Intravenous	1×10^6 cells/kg of body weight, 98% viability	0.31% $CD34^+$ (Mean 62.8×10^6 cells)	10	No serious adverse events were observed during the study	No significant difference in clinical improvement between the groups Increase in the expression of VEGF and BDNF
14	Vahidy et al. (2019)	A phase I, single-arm trial	2 ml/kg (166.3 ± 34.1 ml)	24–72 h after symptom onset	Intravenous	$9.1 \pm 1.6 \times 10^6$/kg of body weight, 96.2% ± 1.9% viability	3.1% ± 0.9% $CD34^+$, 2.3 ± 0.7% Lin^-CD34^+, 1.3 ± 0.5% $Lin^-CD34^+CD133^-$, 1.8 ± 0.6% $Lin^-CD34^+CD133^+$, 31 ± 8.5% lymphocyte, 3 ± 1.6% monocyte, 46.4 ± 8.5%	25	12% of patients had infarct expansion 4% of patients experienced an episode of relative hypotension	Improvement in NIHSS and mRS scores

BM bone marrow; *BMMNCs* bone marrow–derived mononuclear cells; *HSCs* hematopoietic stem cells; *MSCs* mesenchymal stromal/stem cells; *EPCs* endothelial progenitor cells; *BI* Barthel Index; *NIHSS* National Institutes of Health Stroke Scale; *mRS* modified Rankin Scale; *GM-CSF* granulocyte–macrophage colony-stimulating factor; *MMP* matrix metalloproteinase; *PDGF-BB* platelet-derived growth factor BB; *β-NGF* beta-nerve growth factor; *VEGF* vascular endothelial growth factor; *BDNF* brain-derived neurotrophic factor; *CD* cluster of differentiation; *NA* not applicable; *SD* standard deviation

scores (Battistella et al. 2011; Savitz et al. 2011; Prasad et al. 2012) were observed in stroke patients infused intra-arterially or intravenously with BMMNCs. Intrathecal injection of BMMNCs improved ambulation, hand function, standing balance, walking balance, and functional status(Sharma et al. 2014). These findings specifically indicate that the patients did not demonstrate deterioration after receiving the treatment. However, improvements are expected to occur over time regardless of poststroke therapy, and the absence of a control group in the study imposes limitations on the conclusions that can be derived. Thus, additional research is necessary to establish the effectiveness of the therapy.

Although promising outcomes were reported in phase I trials, evidence from phase I/II trials using BMMNCs supports only the safety of the treatment and not its effectiveness in improving neurological outcomes for infused cohorts. In 2012, Moniche et al. reported no significant difference in BI or mRS scores or neurological function at 6 months postinjection between a group intra-arterially injected with an average of 1.59×10^8 BMMNCs and a control group (10 patients per group) in a single-blind controlled phase I/II trial (Moniche et al. 2012). In addition, in a phase II, randomized, multicenter, open-label trial, Prasad et al. (2014) showed no significant differences in NIHSS, BI, or mRS scores between a group infused intravenously with $280.75 \pm 162.9 \times 10^6$ BMMNCs and a control group (Prasad et al. 2014). In 2016, Bhasin et al. reported that no significant clinical improvements were observed either in patients who were intravenously infused with BMMNCs (1×10^6 cells/kg of body weight) or in a placebo control group (10 patients per group) in a randomized placebo-controlled clinical trial (Bhasin et al. 2016). Nevertheless, the numbers of patients in these three studies were small; thus, further randomized studies should be performed to draw accurate conclusions on the effectiveness of BMMNCs for the treatment of stroke.

BMMNCs in the Treatment of CP

CP was first described by William Little in 1862 as a syndrome of motor impairment that is often accompanied by disturbances of sensation, perception, cognition, communication, and behavior; epilepsy; and secondary musculoskeletal problems (Rosenbaum et al. 2007; Colver et al. 2014). Despite advancements in modern medicine, infants with CP carry major risks of complications and a high mortality rate (Blair et al. 2019).

To date, eight clinical studies and case reports, with a total of 191 patients, have demonstrated the safety and efficacy of BMMNCs in the treatment of CP (Table 2). The number of administered BMMNCs ranged from 15 to 120×10^6 cells, or, where a cell dose was reported instead, the dose was 1×10^6 cells/kg of body weight; all cells were infused via the intrathecal route. No adverse events related to BMMNC administration were recorded. In three case studies, Sharma et al. reported that a single administration of BMMNCs improved Functional Independence Measure (FIM) and intelligence quotient (IQ) scores and significantly increased metabolic activity in the brains of CP patients (Sharma et al. 2012, 2013e, 2015c). Mancias-Guerra C et al. demonstrated that CP patients who received BM injections showed an increase in Battelle Developmental Inventory (BDI) scores, including adaptive, personal social, motor, communication, cognitive and developmental age scores (Mancías-Guerra et al. 2014). BMMNC administration also improved neurological function, including oromotor and neck control; sitting, standing and working balance; and speech function (Sharma et al. 2015b); significantly enhanced gross (Liu et al. 2017; Liem et al. 2017; Nguyen et al. 2018; Thanh et al. 2019) and fine motor function (Liu et al. 2017); reduced muscle tone (Thanh et al. 2019); and improved quality of life (Nguyen et al. 2018) in children with spastic CP (Liu et al. 2017) or CP related to neonatal icterus (Thanh et al. 2019) and oxygen deprivation (Liem et al. 2017; Nguyen et al. 2018). In addition, autologous BMMNC administration was safe and feasible, potentially improved cognition (Liem et al. 2020a) and motor function, and reduced muscle spasticity for children in a persistent vegetative state after drowning (Liem et al. 2020a) and children with intracranial hemorrhage incidence that occurred during the neonatal period (Liem et al. 2020b).

In summary, BMMNC therapy is a very promising strategy for the treatment of CP. However, results have been reported for only one randomized clinical trial. Thus, more extensive clinical studies are needed to better understand the effects of BMMNCs as a treatment for CP.

BMMNCs in the Treatment of SCI

SCI is defined as damage to the spinal cord. SCI can directly affect the mobility and physiological condition of patients and lead to paraplegia or tetraplegia, and this type of injury is associated with a high rate of mortality. The annual incidence of SCI worldwide is approximately 250,000 to 500,000 patients (WHO 2020). The past several decades have been a remarkable time for the development of SCI treatment, as numerous pharmacological, neuroprotective, and neuroregenerative therapies have been translated from preclinical models into clinical trials, including cell-based therapy (Wang et al. 2021).

BMMNCs are among the cell types that have been used in the treatment of SCI. Four clinical trials, with a total of 202 patients, have reported the outcomes of therapies in which these cells were injected locally or intrathecally (Table 3).

Table 2 Clinical applications of BMMNCs in the treatment of CP

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
1	Sharma et al. (2012)	A single case report	100 ml, G-CSF	2 years after diagnosis	Intrathecal	12×10^7 cells	$CD34^+$ cells were counted, but the number of cells was not provided	1	No adverse events were recorded	Functional improvement along with changes in PET scan results
2	Sharma et al. (2013e)	A single case report	100 ml, G-CSF	19 years after diagnosis	Intrathecal	1×10^6/kg body weight, 98% viability	$CD34^+$ cells were counted, but the number of cells was not provided	1	No adverse events were reported	Improvement in FIM and IQ scores and metabolic activity 6 months after cell administration
3	Mancias-Guerra et al. (2014)	An open-label, nonrandomized phase I clinical trial	8 ml/kg (up to 150 ml), G-CSF	NA	Double route: intrathecal and then intravenous concurrently	Intrathecal: nucleated 13.12×10^8 (range, 4.83–53.87), 83.6% viability Intravenous: 6.01×10^8 (range, 1.36–17.85), 89.45% viability	Intrathecal: 10.02×10^6 (range, 1.02–29.9) $CD34^+$ Intravenous: 3.39×10^6 (range, 1.36–17.85) $CD34^+$	18	2 patients experienced anesthesia-related adverse events, and 3 patients had side effects after the procedure	No change in MRI Significant increase in BDI scores ($+4.6\pm3.2$ adaptive, $+8.2\pm8.4$ personal social, $+3.5\pm3.8$ motor, $+3.2\pm1.7$ communication, $+4.8\pm4.8$ cognitive, and $+4.7\pm2.6$ developmental age, mean ± SD) in patients
4	Sharma et al. (2015c)	A case report	100 ml, G-CSF	12 years after diagnosis	Intrathecal	3.3×10^7 cells, 98% viability	$CD34^+$ cells were counted, but the number of cells was not provided	1	No adverse events were reported	Functional improvement and increase in FIM score

Table 2 (continued)

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
5	Sharma et al. (2015b)	An open-label, nonrandomized clinical trial	80–100 ml, G-CSF	NA	Intrathecal	10.23×10^6, 98% viability	$CD34^+$ cells were counted, but the number of cells was not provided	40	15% of patients had a spinal headache, 7.5% had nausea, 30% experienced vomiting, 12.5% had pain at the injection site, and 2.5% had diarrhea within a week	At 3-month follow-up: 35% had improvement in oromotor control, 27.5% in neck control, 42.5% in sitting balance, 37.5% in standing balance, 22.5% in working balance, and 30% in speech function At the 6-month follow-up, 95% patients showed improvement
6	Liu et al. (2017)	A randomized controlled clinical trial	45 ml	NA	Intrathecal	1×10^6 cells/kg; four doses at 3- to 4-day intervals	NA	35	8.8% patients had fever, and 17.6% had reactions related to low intracranial pressure	12 months after transplantation, GMFM and FMFM scores were significantly improved
7	Nguyen et al. (2017)	An open-label, uncontrolled clinical trial, phase I	8 ml/kg for patients ≤ 10 kg; [80 + (kg of BW—10) × 7] ml for patients > 10 kg, less than 200 ml	NA	Intrathecal	1st injection: 27.2×10^6 cells, 97.8% viability 2nd injection: 17.1×10^6 cells, 72% viability, 3-month interval	$CD34^+$: 1st dose: 2.6×10^6 cells 2nd dose: 1.1×10^6 cells	40	No severe complications were recorded during the study	Increase in GMFM scores and decrease in muscle tone at 3 and 6 months after transplantation
8	Nguyen et al. (2018)	An open-label, uncontrolled clinical trial	8 ml/kg for patients ≤ 10 kg; [80 + (kg of BW—10) × 7] ml for patients > 10 kg, less than 350 ml	NA	Intrathecal	1st injection: $467 \pm 195 \times 10^6$ cells 2nd injection: $477 \pm 196 \times 10^6$ cells	$CD34^+$: 1st dose: $36 \pm 23 \times 10^6$ cells 2nd dose: $36 \pm 22 \times 10^6$ cells	30	No serious adverse events or severe complications during or after the infusion procedure	Improvement in patients' gross motor function and quality of life

Table 2 (continued)

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
9	Nguyen et al. (2019)	An open-label, uncontrolled clinical trial	8 ml/kg for patients ≤ 10 kg; [80 + (kg of BW—10) × 7] ml for patients > 10 kg, less than 200 ml	NA	Intrathecal	1st injection: $17.4 \pm 11.9 \times 10^6$ cells, 96.6% viability 2nd injection: $15 \pm 12.8 \times 10^6$ cells, 71% viability	$CD34^+$: 1st dose: $1.5 \pm 1.4 \times 10^6$ cells 2nd dose: $1.1 \pm 1.1 \times 10^6$ cells	25	No severe complications occurred during the study period	Increase in GMFM scores after 6 and 12 months and reduced muscle tone values after 12 months

BM bone marrow; *BMMNCs* bone marrow–derived mononuclear cells; *PET* positron emission tomography–computed tomography; *FIM* Functional Independence Measure; *BDI* Battelle Developmental Inventory; *GMFM* Gross Motor Function Measure; *FMFM* Fine Motor Function Measure; *MRI* magnetic resonance imaging; *G-CSF* granulocyte colony-stimulating factor; *IQ* intelligence quotient; *CD* cluster of differentiation; *SD* standard deviation; *BW* body weight

The numbers of BMMNCs used were considerably different among studies, ranging from 106 to 1000×10^6 cells. A study conducted by Suzuki et al. in 2014 showed that intrathecal BMMNC administration was safe in patients with SCI. However, the effectiveness of the treatment was not well substantiated, with only 40% of treated patients showing improvement in Abbreviated Injury Scale (AIS) Scores (Suzuki et al. 2014). More recently, newly published results from an open-label study in which approximately 1.06×10^8 BMMNCs were delivered intrathecally to 180 patients with subacute and chronic SCI demonstrated that BMMNC administration was safe and improved functional recovery as well as patient's quality of life (Sharma et al. 2020a). Two other trials used BMMNCs in combination with an artificial scaffold (NeuroRegen) to investigate neurological recovery for chronic SCI. Their results indicated that the sensory and autonomic nervous function of treated SCI patients were partially improved, but motor function was not, suggesting that the NeuroRegen scaffold together with BMMNC administration contributed to spinal cord structural recovery and continuity after treatment (Xiao et al. 2016; Chen et al. 2020).

BMMNCs in the Treatment of TBI

TBI is a major global health issue causing trauma-related death, especially among young individuals (Rosenfeld et al. 2012). TBI is characterized by reduced blood–brain barrier (BBB) permeability and prolonged microglial activation leading to continued production of proinflammatory and potentially cytodestructive molecules (Cassidy et al. 2004).

Recently, cell-based therapy, including the use of BMMNCs, has been demonstrated to be safe and effective in patients with TBI (Table 4). The safety and efficacy of BMMNCs have been illustrated in four clinical trials, with a total of 95 TBI patients treated. The BMMNCs were injected mainly through the intravenous route, with a dose ranging from 6 to 12×10^6 cells/kg of body weight in 3 clinical trials (Cox Jr et al. 2011, 2017; Liao et al. 2015) and an average of 128×10^6 injected cells per patient in the remaining trial (Sharma et al. 2020e).

One of the first clinical trials of BMMNCs for the treatment of TBI was conducted in 10 pediatric patients (Cox Jr et al. 2011), and this trial was followed by a retrospective cohort study of 10 patients (Liao et al. 2015) with TBI. These two studies illustrated that BM aspiration in children with TBI is safe and feasible. No severe adverse events—in fact, no adverse events at all—were reported in association with BMMNC infusion. A progressive improvement in clinical outcomes was detected 6 months after administration (Cox Jr et al. 2011). By using the Pediatric Intensity Level of Therapy (PILOT) and Pediatric Logistic Organ Dysfunction (PELOD) scales, the retrospective study provided

Table 3 Clinical applications of BMMNCs in the treatment of SCI

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
1	Suzuki et al. (2014)	A nonrandomized, uncontrolled phase I/II trial	120 ml	129.5 ± 31 days after injury (24–194 days)	Intrathecal	$4.1 \pm 1.9 \times 10^8$ cells	24.7 ± 5.9% $CD11b^+$, 25.7 ± 4.5% $CD11c^+$, 91.4 ± 11.1% $CD29^+$, 23.4 ± 7.9% $CD34^+$, 80.1 ± 32.6% $CD45^+$, 10.9 ± 10.8% $CD90^+$, 30 ± 12.2% $CD117^+$, 11 ± 4.7 $CD133^+$	10	Two patients showed slight anemia after BM aspiration, which resolved within several weeks	4/10 patients showed an improved AIS score and the AIS scores of 6/10 patients were maintained 6 months after transplantation
2	Xiao et al. (2016)	A nonrandomized, uncontrolled phase I/II trial	50 ml	13 ± 5.1 months (2–32 month) after injury	Local implantation	1×10^9 cells	NA	5	No obvious adverse events related cell infusion were observed	Autonomic neural function was improved, no change in ASIA impairment grade
3	Sharma et al. (2020a)	An open-label clinical trial (Phase 1)	80–100 ml, G-CSF	NA	Intrathecal	An average of 1.06×10^8 cells, 97% viability	CD34 + cells were counted, but the number of cells was not provided	180	No serious adverse events were observed	69.44% and 37.22% of patients showed improved FIM and WISCI scores, respectively Improvement in AISA grade and symptoms
4	Chen et al. (2020)	A nonrandomized, uncontrolled phase I/II trial	200 ml	8.7 ± 3.1 days (3–27 days) after injury	Local implantation	1×10^9 cells	0.1% $CD34^+$	7	No obvious adverse events were observed in 36 months of follow-up	Significant improvements in FIM, ADL, and VAS scores; no significant improvements in AISA motor score or function

BM bone marrow; *BMMNCs* bone marrow–derived mononuclear cells; *FIM* Functional Independence Measure; *WISCI* Walking Index for Spinal Cord Injury; *AIS* Abbreviated Injury Scale; *ASIA* American Spinal Injury Association; *ADL* activities of daily living; *VAS* visual analog scale; *G-CSF* granulocyte colony-stimulating factor; *CD* cluster of differentiation; *SD* standard deviation

foundational data supporting the use of the treatment for inflammation-associated cerebral edema as well as the BBB permeability of the BMMNCs. Moreover, the study directly compared the outcomes of each individual and the corresponding time-matched control with the outcomes of the treatment group reported in the initial trial (Liao et al. 2015; Cox Jr et al. 2011). In a phase I/II trial, 25 adults with TBI were divided into 3 groups who received BMMNCs at three different doses: 6×10^6, 9×10^6, and 12×10^6 BMMNCs per kg of body weight (Cox Jr et al. 2017). This study confirmed the safety of BMMNCs infused via either peripheral or central venous catheters and demonstrated the efficacy of the treatment through improvements in neurocognitive outcomes and reductions in proinflammatory cytokine responses (Cox Jr et al. 2017). Recently, the results from an open-label, nonrandomized study of intrathecally delivered BMMNCs in 50 patients with chronic TBI supported the safety of BMMNC treatment (Sharma et al. 2020e). Overall, 92% of patients showed improvements in motor function (sitting and standing balance), memory, ambulation, trunk and upper limb activity, communication, psychological status, cognition, and quality of life. A positron emission tomography–computed tomography (PET-CT) scan demonstrated improvements in brain metabolism in areas correlated with TBI (Sharma et al. 2020e). Taken together, the data from recent and ongoing clinical trials on the treatment of TBI using BMMNCs supports the safety of cell-based therapy and demonstrates that BMMNCs reduce the neuroinflammatory response to injury. At present, there are two phase IIb trials being conducted in children and adults using a Bayesian adaptive design to compare two doses of BMMNCs to a control; imaging end points are being used as the putative biomarkers of efficacy. When these two trials are completed, the results will definitely provide further information and insights into the mechanism underlying the efficacy of BMMNCs (Cox 2018).

BMMNCs in the Treatment of ALS

ALS is a chronic degenerative disease mainly affecting motor neurons and lung function in adults. The annual incidence and prevalence of ALS are approximately 1–1.2 cases and 6 cases, respectively, per 100,000 people worldwide (Talbott et al. 2016). Multidisciplinary palliative care is required to improve patients' quality of life (Hardiman et al. 2011).

BMMNCs have been used in 7 clinical trials and case reports (72 patients in total) for the treatment of ALS (Table 5). The cells were mainly injected intrathecally in numbers ranging from 80 to 460×10^6 cells per patient. In 2012, a phase I study by Blanquer et al. demonstrated the neurotrophic activity of BMMNCs, as evidenced by reduced motoneuron degeneration in ALS patients following BMMNC infusion into the posterior funiculus of the spinal cord (Blanquer et al. 2012). The functional status of ALS patients who received intrathecal BMMNC administration tended to be preserved, as stable ALS Functional Rating Scale (ALSFRS) scores were observed 3 months after treatment (Prabhakar et al. 2012). A retrospective study by Sharma et al. demonstrated that intrathecal infusion of BMMNCs increased the survival duration of ALS patients (Sharma et al. 2015d). Intramedullary injection of BMMNCs for patients with ALS has been demonstrated to be safe and does not worsen the disease (Ruiz-López et al. 2016). Case reports illustrated that intrathecal BMMNC administration combined with lithium, riluzole, and rehabilitation slowed ALS progression and improved motor function and ALSFRS scores in one study (Sane et al. 2016); maintained FIM and Berg Balance Scale scores in another study (Sharma et al. 2019); and mitigated ALS disease progression, increased 6-min walk test performance, and improved the condition of the patient in a third study (Sharma et al. 2020c).

Although BMMNCs were associated with some beneficial effects, most of the previously mentioned clinical studies were case reports and pilot studies with small numbers of participants and no control groups. Thus, further studies with control groups and larger sample sizes should be performed to corroborate the evidence for the efficacy of BMMNCs in treating this disease.

BMMNCs in the Treatment of ASD

ASD is a complex spectrum disorder with two main aspects: (1) deficits in social communication and interaction and (2) restricted interests as well as repetitive and stereotypic behaviors. Currently, there is no curative treatment for autism in practice. Different clinical trials using cell therapies are being performed (Mukherjee 2017).

To our knowledge, only two research groups, one in Vietnam and the other in India, with a total of 9 clinical trials and case reports, have applied BMMNCs for ASD treatment (Table 6). In these studies, a total of 322 ASD patients were intrathecally infused with BMMNCs, with the number of cells ranging from 56 to 145×10^6 cells or the dose of cells ranging from 18 to 42×10^6 cells/kg of body weight.

Sharma et al. (2013a) reported the case of a 14-year-old boy with severe ASD who was intrathecally injected with BMMNCs. At the 6-month follow-up, his Childhood Autism Rating Scale (CARS) score had improved from 42.5 to 23.5, and a PET-CT scan revealed improved brain function (Sharma et al. 2013a). The Sharma group also performed an open-label proof-of-concept study of BMMNC administration in 32 patients with ASD; they found that the Indian Scale for Assessment of Autism (ISAA) scores of 91% of patients improved, as did the Clinical Global Impression

Table 4 Clinical applications of BMMNCs in the treatment of TBI

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
1	Cox Jr et al. (2011)	An open-label, nonrandomized, uncontrolled phase I trial	3–5 ml/kg body weight	Within 48 h after TBI	Intravenous	6×10^6 cells/kg, 98% viability	$4.12\pm0.59\%$ $CD34^+$; 1.36 ± 0.1 Lin^-CD34^+; 0.63 ± 0.09 $Lin^-CD34^+CD133^-$; 0.87 ± 0.09 $Lin^-CD34^+CD133^+$; 15.44 ± 1.29 T cells; 7.89 ± 1.12 B cells; 2.71 ± 0.46 NK cells	10	There was no BM-harvest-related hemodynamic depression or infusion-related toxicity	Dichotomized Glasgow Outcome Scale scores at 6 months showed good outcomes in 70% of patients and moderate to severe disability in 30%. No reduction in volumes of gray or white matter or CSF
2	Liao et al. (2015)	A retrospective cohort study	3–5 ml/kg body weight	Within 48 h of injury	Intravenous	6×10^6 cells/kg	NA	10	No adverse events were reported	Reduction in PILOT and PELOD scores, improvement in Glasgow Coma Scale scores, and decrease in ICP values
3	Cox Jr et al. (2017)	An open-label, nonrandomized, single-center clinical trial (phase I/II)	3–5 ml/kg body weight	Within 36 h of injury	Intravenous	3 different doses: 6×10^6 cells/kg, $94.4\pm1.4\%$ viability, 9×10^6 cells/kg, $96.9\pm0.9\%$ viability, 12×10^6 cells/kg, $98.2\pm0.5\%$ viability	For 6×10^6 cells/kg dose: $1.9\pm0.4\%$ $CD34^+$, $65.4\pm4.6\%$ T cells, $19.6\pm4.2\%$ B cells, $10.8\pm1.4\%$ NK cells For 9×10^6 cells/kg dose: $2.1\pm0.3\%$ $CD34^+$, $72.7\pm2.5\%$ T cells, $13.3\pm3.4\%$ B cells, $9.2\pm1.4\%$ NK cells For 12×10^6 cells/kg: $1.9\pm0.2\%$ $CD34^+$, $70.8\pm3\%$ T cells, $14.9\pm2.5\%$, $7.2\pm1.4\%$ NK cells	15	No major or serious adverse events during BM harvest or cell infusion were reported	Key inflammatory cytokines were downregulated after cell infusion

Table 4 (continued)

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
4	Sharma et al. (2020e)	An open-label, nonrandomized clinical study	80–100 ml, G-CSF	NA	Intrathecal	1.28×10^8 cells, 97% viability	$CD34^+$ cells were counted, but the number of cells was not provided	50	Two patients had seizure episodes (1 patient had a previous history), which were managed with medication	Improvement in symptoms (92%), grade (90%), FIM scores (60%), and brain metabolic activity in all tested patients (10)

BM bone marrow; *BMMNCs* bone marrow–derived mononuclear cells; *PILOT* Pediatric Intensity Level of Therapy; *PELOD* Pediatric Logistic Organ Dysfunction; *FIM* Functional Independence Measure; *ICP* intracranial pressure; *CSF* cerebrospinal fluid; *G-CSF* granulocyte colony-stimulating factor; *CD* cluster of differentiation; *NK* natural killer; *SD* standard deviation; *NA* not applicable

(CGI) scale scores of 62% of patients(Sharma et al. 2013c). Case reports demonstrated that BMMNC infusion combined with neurorehabilitation improved ISAA, CGI, CARS, and Pediatric Functional Independence Measure (WeeFIM) scores and led to a balancing effect on brain metabolism in patients with ASD (Sharma et al. 2013b, d, 2015a, 2017, 2018). Similar results were also obtained in a recent study in which 254 ASD patients received BMMNC infusions in combination with neurorehabilitation (Sharma et al. 2020d). More interestingly, the authors found that younger patients and shorter disease duration were correlated with better outcomes from the intervention, while sex did not influence the outcome (Sharma et al. 2020d). In 2020, a clinical trial by Nguyen et al. in 30 ASD patients demonstrated that BMMNC infusion in combination with behavioral intervention was safe and well tolerated. BMMNC administration reduced CARS scores; increased Vineland Adaptive Behavior Scale scores; and remarkably improved social communication, daily skills, and language (Nguyen Thanh et al. 2021).

Currently, educational intervention is a routine therapy for patients with ASD. Although there is evidence showing beneficial effects of BMMNC administration when combined with neurorehabilitation, the studies are limited by their small sample sizes. Additionally, the absence of control groups in the studies makes it difficult to draw an accurate conclusion about the effects of BMMNCs on ASD.

BMMNCs in the Treatment of Epilepsy

Epilepsy is a chronic neurological disorder affecting 0.5–1% of the population worldwide (Engel Jr 2001). Although pharmacological intervention using antiepileptic drugs is the mainstay of epilepsy treatment, almost 30% of cases are refractory to this treatment. Furthermore, antiepileptic drugs merely provide symptomatic treatment; they do not influence the disease itself. Alternative strategies, including surgery and a ketogenic diet, are sometimes infeasible or only partially effective for patients (Dalic et al. 2016).

Although numerous preclinical studies in which BMMNCs were administered to animals with epilepsy showed promising results, there have been limited numbers of clinical studies using BMMNCs for patients with epilepsy (2 clinical trials with a total of 24 patients infused) (Table 7). In 2018, DaCosta et al. demonstrated the safety and feasibility of intra-arterial infusion of BMMNCs in 20 adult patients with medically refractory mesial temporal lobe epilepsy and unilateral hippocampal sclerosis (DaCosta et al. 2018). At 6 months after infusion, 40% of the patients were seizure free, and memory scores were also increased. Milczarek and colleagues studied a regimen consisting of a single BMMNC infusion combined with four autologous MSC administrations in four children with drug-resistant

Table 5 Clinical applications of BMMNCs in the treatment of ALS

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
1	Blanquer et al. (2012)	An open single-arm phase I trial	60 ml	24.64 ± 2.8 months (14–40 months) after diagnosis	Intraspinal	426×10^6 80% viability	0.6% $CD34^+$, 0.5% $CD117^+$, 0.3% $CD133^+$	11	No severe adverse events observed	Reduction in motoneuron degradation
2	Prabhakar et al. (2012)	An open-label pilot study	103 ± 12.8 ml	Median duration of 16 months (3–48 months) after diagnosis	Intrathecal	$1.81 \pm 0.92 \times 10^8$, 91 ± 2.6% viability	$3.44 \pm 1.58 \times 10^6$ $CD34^+$	10	No significant adverse events were reported	Maintenance of ALSFRS scores for 3 months after administration
3	Sharma et al. (2015d)	A retrospective controlled study	100–120 ml	87.76 ± 10.45 months (13–158 months) after diagnosis	Intraspinal	80.5×10^6 96.7% viability	$CD34^+$ cells were counted, but the number of cells was not provided	37	No cell-infusion-related adverse events were reported	Increase in survival duration
4	Ruiz-López et al. (2016)	An open-label single-arm phase I trial	NA	22.81 ± 2.73 months (range 15–40 months) after diagnosis	Intramedullary	NA	NA	11	No adverse events were reported	Decrease in REM sleep one year after injection but not significantly and no difference in apnea–hypopnea index, mean oxygen saturation or nadir desaturation evolution
5	Sane et al. (2016)	A case report	100 ml	3 years after diagnosis	Intrathecal	460×10^6, 98% viability	$CD34^+$ cells were counted, but the number of cells was not provided	1	No adverse events were reported	Improvement in neurological symptoms Slowed progression of ALS (ALSFRS scores dropped 8% over 17 months after injection, and FIM scores remained stable)

Table 5 (continued)

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
6	Sharma et al. (2019)	A case report	110 ml, G-CSF	2 years after diagnosis	Intrathecal	2 doses: 1st dose: 88×10^6, 98% viability 2nd dose: 208×10^6, 98% viability	6.36% $CD34^+$ 6.48% $CD34^+$	1	No adverse events were noted	Improvements in symptoms and ALSFRS scores; stability of FIM and Berg Balance Scale scores
7	Sharma et al. (2020c)	A case report	110 ml, G-CSF	4 years after diagnosis	Intrathecal	120×10^6, 98% viability (1st) 160×10^6, 98% viability (2nd) 350×10^6, 98% viability (3rd)	5.35% $CD34^+$ 2.06% CD34 3.02% CD34	1	No irreversible adverse events were reported after transplantation	Improvement in six-minute walk test performance, stability of ALSFRS-R scores, decrease in FIM scores, increase in gross motor skills

BM bone marrow; *BMMNCs* bone marrow–derived mononuclear cells; *ALSFRS(-R)* ALS Functional Rating Scale(–Revised); *FIM* functional independence measure; *REM* rapid eye movement; *G-CSF* granulocyte colony-stimulating factor; *CD* cluster of differentiation; *SD* standard deviation; *NA* not applicable

Table 6 Clinical applications of BMMNCs in the treatment of ASD

Order	Author	Study design	Volume of aspirated BM, mobilizer	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
1	Sharma et al. (2013a)	A case report	100 ml, G-CSF	14 years after diagnosis	Intrathecal	56×10^6, 98% viability	1.92% $CD34^+$	1	No side effects were observed	Improvements in eye contact, attention, handwriting, and fine motor function within a week Reductions in CARS score and hyperactivity; improvements in reading skill, tracing, behavior, and PET-CT findings
2	Sharma et al. (2013c)	An open-label proof-of-concept study	80–100 ml, G-CSF	7.17 ± 4.2 years (0–18 years) after diagnosis	Intrathecal	81.9×10^6, 97% viability	$CD34^+$ cells were counted, but the number of cells was not provided	32	No complications were observed during the procedure A few patients showed minor adverse events, such as headache, nausea, vomiting, backache and pain, during their hospital stays. Three patients had seizures	Improvement in ISAA (91% patients) and CGI-II scores (96.9%), reduction in CGI-I scores (62%) Improvements in symptoms, emotional responsiveness, social relationships, sensory processing, attention, concentration, language, speech, behavior, and communication
3	Sharma et al. (2013b)	A case report	100 ml G-CSF	15 years after diagnosis	Intrathecal	56×10^6, 98% (1st) viability 56×10^6, 98% (2nd) viability	$CD34^+$ cells were counted, but the number of cells was not provided	1	No side effects were observed	Improvements in ISAA and CGI scores, social relationships, behavior, language, and communication A PET-CT scan revealed a balancing effect on the metabolism of affected areas

Table 6 (continued)

Order	Author	Study design	Volume of aspirated BM, mobilizer	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
4	Sharma et al. (2013d)	A case report	100 ml G-CSF	10.5 years after diagnosis	Intrathecal	56×10^6, 96% viability	$CD34^+$ cells were counted, but the number of cells was not provided	1	No adverse events were recorded	Improvements in social relationships, communication, behavior, ISAA score, and PET-CT scan findings at 18 months postinjection
5	Sharma et al. (2015a)	A case report	100 ml G-CSF	7 years after diagnosis	Intrathecal	96×10^6, 96% viability	$CD34^+$ cells were counted, but the number of cells was not provided	1	No adverse events were reported	Improvements in behavior; social relationships; communication; cognition; ISAA, CARS, and CGI scores; PET-CT findings; and WeeFIM scores at 3 and 6 months posttreatment
6	Sharma et al. (2017)	A case report	100 ml G-CSF	3.5 years after diagnosis	Intrathecal	96×10^6, 96% viability	$CD34^+$ cells were counted, but the number of cells was not provided	1	No major side effects were observed	Improvements in symptoms and CARS, ISAA, and WeeFIM scores 7 months after treatment PET-CT changes were correlated with clinical improvement

Table 6 (continued)

Order	Author	Study design	Volume of aspirated BM, mobilizer	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
7	Sharma et al. (2018)	A case report	100 ml G-CSF	18 years after diagnosis	Intrathecal	145×10^6, 96% viability	6.3% $CD34^+$	1	No adverse events were recorded	Improvements in concentration, attention, command following, sitting tolerance, social interactions, eye contact, and memory. Reductions in ISAA, CARS, and FIM scores. Improvements in PET-CT scan findings 6 months posttreatment
8	Sharma et al. (2020d)	An open-label, nonrandomized longitudinal study	80–100 ml G-CSF	From 0 to more than 5 years after diagnosis	Intrathecal	NA	$CD34^+$ cells were counted, but the number of cells was not provided	254	Procedure-related adverse events included headache, nausea, diarrhea, vomiting, and pain or bleeding at the aspiration/injection site Transplantation-related adverse events: 1.9% of patients experienced seizures	More than 80% of patients showed improvements in sitting tolerance, command following, attention, concentration and eye contact More than 60% of patients showed improvements in social interaction, hyperactivity, speech, and communication More than 50% of patients showed reduced self-injurious and stereotypic behaviors as well as reduced aggressiveness ISAA (94.27%) and CARS (95.27%) scores were reduced as well

Table 6 (continued)

Order	Author	Study design	Volume of aspirated BM, mobilizer	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
9	Nguyen et al. (2021)	An open-label uncontrolled clinical trial	8 ml/kg for patients ≤ 10 kg; [80 + (kg of body weight—10) × 7] ml for patients > 10 kg, less than 200 ml	NA	Intrathecal	42.3×10^6/kg, 98% viability (1st) 40.9×10^6/kg, 99% viability (2nd)	6.15% $CD34^+$ 5.13% $CD34^+$	30	27.1% of patients had intervention-related adverse events, including pain, ruptured veins, peripheral vein masonry, and slippage of the needle from the vein	Decrease in ASD severity and CARS scores Improvements in social communication, language and daily skills

BM bone marrow; *BMMNCs* bone marrow–derived mononuclear cells; *PET-CT* positron emission tomography–computed tomography; *CARS* Childhood Autism Rating Scale; *ISAA* Indian Scale for Assessment of Autism; *CGI* Clinical Global Impression; *WeeFIM* Pediatric Functional Independence Measure; *G-CSF* granulocyte colony-stimulating factor; *CD* cluster of differentiation; *SD* standard deviation; *NA* not applicable

epilepsy (Milczarek et al. 2018). Although no improvement was shown after BMMNC infusion, the findings indicated that the combination was safe and feasible. BMMNC and MSC treatments were associated with considerable neurological and cognitive improvement (Milczarek et al. 2018). Further studies should be conducted to evaluate the efficacy of BMMNCs in the treatment of epilepsy.

Harvesting Procedures, Administration Routes and Doses of BMMNCs

BM Harvesting Procedures

BM can be aspirated from the posterior iliac crest and anterior iliac crest. The choice between these two sites largely depends on standard practice at individual centers. However, the collection of BM from the posterior iliac crest in the prone position is associated with some risk during anesthesia and is less comfortable for patients. Thus, the anterior iliac crest might be considered a better choice to address these disadvantages (Reed et al. 2018).

The volume of BM aspirated varied depending on the study and disease. It seems that the aspirated volume is largely contingent on hemodynamics. In general, the volume of aspirated BM for the treatment of neurological diseases varies widely, ranging from 25 to 200 ml, or depends on the body weight of patients. In some studies, the volume of aspirated BM that authors collected was based on body weight, such as 2 ml/kg in stroke patients (Table 1), 8 ml/kg in pediatric CP patients under 10 years old (Table 2), or 3–5 ml/kg in TBI patients (Table 4). It was reported that the average number of BMMNCs per milliliter and the percentage of $CD34^+$ cells were sex dependent, as these values were lower in females than in males, and there was a dramatic reduction in the number of $CD34^+$ cells in females in the older age group (Dedeepiya et al. 2012).

It was also shown that the number and functionality of BMMNCs were reduced by age, leading to a reduction in the effectiveness of autologous BMMNCs in regenerative medicine (Beausejour 2007). Thus, the volume of aspirated BM needs to be considered. The lower the volume of aspirated BM, the fewer BMMNCs it will yield. Hence, the volume of aspirated BM and the number of collected BMMNCs must be balanced so that the desired efficacy of the treatment will be achieved without impairing the patient's general health condition. Thus, the intervention should be carefully performed by well-trained personnel. Nguyen et al. demonstrated that the aspiration of 8 ml BM/kg of body weight was safe in children (Nguyen Thanh et al. 2021), while Cox et al. showed that the aspiration of a maximum of 5 ml BM/kg of body weight was safe in adults (Cox Jr et al. 2017).

Thus, we suggest that those volumes could be collected to yield the maximum number of BMMNCs.

The administration of granulocyte colony-stimulating factor (G-CSF) prior to BM harvest is well known to mobilize the cells and increase the number of cells harvested. The stroke studies did not include the injection of G-CSF before BM harvest except for Sharma et al.'s study in 2014 (Sharma et al. 2014). This group also used G-CSF in CP patients before BMMNC aspiration (Sharma et al. 2012, 2015c, 2013e). Evidence has shown that G-CSF has negative effects associated with increased brain atrophy and exaggerated inflammatory responses in a mouse model (Taguchi et al. 2007). In addition to its effect on HSC mobilization, G-CSF increased the accumulation of activated macrophages/microglia in the brain, which has been demonstrated to cause brain damage in an experimental stroke model by enhancing inflammation at the site of cerebral ischemia (Taguchi et al. 2007). Furthermore, there is a concern regarding diminished potency in mobilized HSCs (Patterson and Pelus 2017). The injection of G-CSF prior to BM cell administration has also been reported to cause low-grade fever and irritability due to bone aches in some CP patients (Mancías-Guerra et al. 2014). Thus, the use of G-CSF to mobilize HSCs before BM harvesting is not recommended.

Doses of BMMNCs Administered

Given the different volumes of BM aspirated, different BMMNC doses were administered in patients with various neurological diseases. Based on published data, the number and dose of administered BMMNCs varied depending on the disease and study: $10–500\times10^6$ cells or $1–10\times10^6$ cells/kg of body weight in stroke patients, $15–120\times10^6$ cells or 1×10^6 cells/kg of body weight in CP patients, $106–1000\times10^6$ cells in SCI patients, an average of 128×10^6 cells or $6–12\times10^6$ cells/kg of body weight in TBI patients, $80–460\times10^6$ cells in ALS patients, and $56–145\times10^6$ cells or $18–42\times10^6$ cells/kg of body weight in ASD patients. Evidence of an association between the quality and/or quantity of infused BMMNCs and potential outcomes was observed. Suarez-Monteagudo C et al. reported that the stroke patient who received the fewest BMMNCs and had the poorest cell survival rate (14×10^6 cells, 50% viability) had inferior neurological and neuropsychological results (Suarez-Monteagudo et al. 2009). In 2015, Taguchi et al. illustrated that stroke patients who received a higher dose (mean 3.4×10^8 BMMNCs/kg body weight) showed better improvement in neurological outcomes than those who received a lower dose (mean 2.5×10^8 BMMNCs/kg body weight) (Taguchi et al. 2015a). However, Cox Jr et al. demonstrated that an infused dose of 6, 9, or 12×10^6 BMMNCs/kg of body weight did not result in different outcomes in TBI patients (Cox Jr et al. 2017).

It is likely that the number of injections influenced the outcomes of BMMNC treatment for neurological diseases. Previous studies showed that an increased number of BMMNC injections in the treatment of CP, SCI, and ALS was associated with superior improvements (Sharma et al. 2020b, 2019, 2020c; Liu et al. 2017; Nguyen et al. 2017; Thanh et al. 2019). Liu et al. administered four injections of BMMNCs at three- to four-day intervals in children with CP and showed improvements in motor function (Liu et al. 2017). Nguyen et al. treated CP patients with two injections of BMMNCs separated by a 3-month (Liem et al. 2017) or 6-month interval (Thanh et al. 2019) and observed an increase in gross motor function scores and a decrease in muscle tone scores after the treatment. Recently, Sharma et al. reported a higher percentage of SCI patients with improvements after two injections of BMMNCs than after a single injection (Sharma et al. 2020b). Two (Sharma et al. 2019) and three injections (Sharma et al. 2020c) of BMMNCs into ALS patients led to improvements in ALS-FRS-R scores, 6-min walking test distance, and symptoms.

However, there was no significant difference in FIM scores between TBI patients who were given two injections and those who were given a single injection, suggesting that the number of BMMNC injections does not affect potential outcomes in the treatment of TBI patients (Sharma et al. 2020f). Nevertheless, the studies were only case reports, and no comparative analysis of the number of injections was performed. Moreover, there is still a lack of direct evidence presenting a correlation between the number of injections and therapy outcomes. Thus, further optimization of the number of injections for each neurological disease is still needed.

Timing of BMMNC Administration

The therapeutic time window for autologous BMMNCs can vary depending on the specific condition being treated. At present, there is too little evidence to establish the optimal time for BMMNC infusion to treat neurological diseases. Previous studies showed that the timing of administration for stroke ranged from 24 h after onset to 144 months post-stroke (Table 1). In CP, the timing of BMMNC administration is not well identified based on current data. Only three studies reported the time window in which BMMNCs were administered to CP patients; in all cases, the treatment was applied at different time points (2, 12, and 19 years after diagnosis) (Table 2). While the time window for the cell therapy of SCI ranged from 2 days to 32 months postinjury (Table 3), BMMNCs were administered within 48 h to treat TBI (Table 4). In almost all clinical studies of BMMNCs for ALS, the duration of disease from diagnosis to cell infusion was 1 to 4 years (Table 5). The time windows of cell therapy for ASD (Table 6) and epilepsy (Table 7) were also very late in almost all cases (ranging from 0 to 15 years

Table 7 Clinical applications of BMMNCs in the treatment of epilepsy

Order	Author	Study design	Volume of aspirated BM	Stem cell administration				No. of BMMNC-treated patients	Safety	Main findings
				Timing of administration	Route	Number or dose of cells, viability	Cell subtype proportions (mean ± SD)			
1	DaCosta et al. (2018)	An open, uncontrolled phase I/II safety study	60 ml	25.4 ± 10.7 years (5 to 47 years) after epilepsy onset	Intra-arterial	1.52–10 × 10^8 cells	2.44 ± 2.15% $CD117^+$, 2.97 ± 1.62% $CD34^+$, 2.78 ± 2.2% $CD117/34^+$, 0.8 ± 0.73% $CD105^+$, 26.16 ± 14.9 $CD45^+$, 4.28 ± 3.87 $CD105/45^+$	20	4/20 patients had headaches on the day of the procedure, 1 patient out of 20 had postictal psychosis during video-EEG monitoring, which was managed by clobazam	Significant increase in memory scores over time At 6 months after treatment, 40% of patients were seizure free; 25%, 15% and 20% had a reduction in the number of seizures by 70–99%, 50–69%, and less than 50%, respectively
2	Milczarek et al. (2018)	A prospective, longitudinal experiment	NA	1 months to 5.5 years after epilepsy onset	Dual: intravenous and intrathecal	Intravenous: 0.5 × 10^8 and Intrathecal: 0.38–1.72 × 10^8	NA	4	No adverse events observed during the 2-year follow-up	No improvement was shown after BMMNC infusion

BM bone marrow; *BMMNCs* bone marrow–derived mononuclear cells; *CD* cluster of differentiation; *NA* not applicable

after diagnosis for ASD and 1 month to 47 years after diagnosis for epilepsy). In general, the earlier the cells are administered after injury, the better the potential for positive outcomes. However, the optimal time window needs to be carefully studied. During acute neurological conditions, there may still be ongoing tissue damage, inflammation, and neuronal death, and the administration of BMMNCs aims to modulate these processes and promote tissue repair and neuroprotection (Yang et al. 2013; Chen et al. 2020; Wang et al. 2021). However, tissue remodeling, neuroplasticity, and functional recovery processes may still be under way during the subacute phase. Thus, BMMNC transplantation supports these regenerative processes and enhances neurological repair (Prasad et al. 2012; Rosado-de-Castro et al. 2013b; Sharma et al. 2020b). BMMNC transplantation in the chronic phase has been explored in both animal studies and clinical trials. While the therapeutic effects may be less pronounced in this phase than in the acute and subacute phases, studies have indicated potential benefits, including improved neurological function and quality of life (Bhasin et al. 2012; Acosta et al. 2015; Sharma et al. 2020f). Overall, it is worth noting that the optimal timing for BMMNC transplantation may differ based on the specific neurological conditions and the stage of the disease, and research is ongoing to determine the optimal timing for different conditions. Additionally, autologous BMMNCs have not yet received approval in most countries for the treatment of neurological conditions, thus, patients should consult with stem cell experts and stay updated on the latest scientific literature when considering autologous BMMNC therapy.

Route of BMMNC Administration

The potential outcomes of cell therapy largely depend on the delivery of the cells to the target organs. In clinical trials, there are different main routes of administration of BMMNCs for neurological diseases, including intravenous, intra-arterial, and intrathecal injections as well as direct injections into the brain or spinal cord. Intravenous administration is an easy and minimally invasive procedure; however, only a few infused cells reach the target tissue because the cells can be trapped in the lungs and other organs (Fischer et al. 2009). Moreover, a concern was recently raised that local thrombosis or lung embolism could occur after HSC infusion via the intravenous route (Zahid et al. 2016). Intra-arterial administration is likely to overcome this limitation (Amar et al. 2003). Intra-arterial administration has the theoretical advantage of selective delivery to the injured brain but is associated with risks of arterial occlusion or embolization (Sudulaguntla et al. 2017). It was reported in one study that BMMNCs started to home to the brain in six out of six stroke patients at 2 h after administration via intra-arterial injection. The remaining cells migrated to the liver, lungs, spleen, kidneys, and bladder (Barbosa da Fonseca et al. 2010). A subsequent study revealed poor distribution (approximately 0.9% of infused BMMNCs) to the brain 24 h after administration (Rosado-de-Castro et al. 2013a).

Intracerebral injection is the most direct method of delivery to the target site. However, this method is rarely used to infuse BMMNCs for the treatment of neurological diseases because it is a risky and invasive procedure. The intrathecal delivery of cells is particularly attractive due to the less invasive nature of the procedure; additionally this method facilitates the migration of cells to the injured site through cerebrospinal fluid (CSF) and the efficient homing of BMMNCs across the BBB in a relatively immune-privileged environment (Bakshi et al. 2004). CSF has also been demonstrated to have properties that support cell growth (Miyan et al. 2006). Indeed, the intrathecal route for children remains controversial. A concern about the safety of this route was raised, as intrathecal injection can lead to serious consequences, such as arachnoiditis and paralysis due to bleeding into the spinal cord (Finlay-Morreale 2021). In fact, this route is routinely used to deliver drugs or local anesthesia and to obtain CSF samples with very low risk (Carness and Lenart 2019; De Andres 2022). Direct administration/local implantation has been used for BMMNC administration in patients with SCI (Xiao et al. 2016). However, this route requires a surgical procedure and is associated with a high risk of bleeding and infection.

Notably, in current practice, the administration route varies depending on the neurological disease. In stroke, various methods, including the intravenous, intra-arterial, intrathecal (Sharma et al. 2014), and intracerebral routes (Suárez-Monteagudo et al. 2009), have been employed for BMMNC administration. Among these administration methods, the intravenous and intra-arterial routes are commonly used. In experimental stroke models, a comparison of intravenous and intra-arterial injection showed no significant difference in the therapeutic effect on functional recovery or cell distribution to other organs, such as the lungs and spleen (Vasconcelos-dos-Santos et al. 2012; Yang et al. 2013). These results suggest that intravenous injection may not be inferior to intra-arterial injection regarding either therapeutic effects or the potential for embolism/deposition in other organs. In addition, while the intravenous route is commonly used for BMMNC administration in TBI, intrathecal administration is the main route for BMMNC administration in patients with CP, ALS, and ASD in all reported studies (Tables 2, 5, 6). Local implantation and intrathecal administration are used for BMMNC injection in SCI (Table 3). However, local implantation is more invasive than other routes. To date, no comparative analysis between administration routes in the same context has been performed. Thus, the correlation between the administration routes and the outcomes

of BMMNC administration is a question for which further investigation is needed.

In summary, it is important to select an ideal administration route that will allow the maximum number of infused cells to reach the target area while being the least invasive. Intrathecal administration allows more infused stem cells to reach damaged areas because they are not trapped in the lungs and spleen as they are when given intravenously. Thus, we suggest that intrathecal administration might be the ideal route for stem cell infusion to treat neurological diseases where infused cells are required to reach damaged areas for recovery. However, more studies are required to identify which route should be used to deliver cells for each disease.

Proposed Mechanisms of BMMNCs in Neurological Diseases

BMMNCs obtained after Ficoll gradient centrifugation of BM to remove granulocytes, red blood cells, and platelets are a heterogeneous population of cells with single round nuclei; these cells include myeloid cells (monocytes, dendritic cells, etc.), lymphoid cells (T, B, and NK cells), and stem cells (HSCs, EPCs, and MSCs). The proportions of these cell types vary depending on the individual and that person's health condition (Zhao et al. 2012). Malliaras and Marban reported very few stem cells (0.01% MSCs and 2–4% HSCs/EPCs) (Malliaras and Marbán 2011) and Muse cells among BMMNCs (Kuroda et al. 2013). Each subpopulation among BMMNCs plays a different role (Table 8) in the main proposed mechanisms, including angiogenesis, neuroprotection, anti-inflammatory effects, and differentiation into target cells. Most studies have focused on the $CD34^+$ population in BMMNCs to investigate the potential efficacy of the treatment. $CD34^+$ cells have been demonstrated to migrate to sites of injury to restore damaged neurons (Callera et al. 2007). However, Dawson and colleagues have demonstrated that frequency of $CD34^+$ cells in cord blood–derived BMMNCs was not correlated with improvement in children with ASD or CP. A study has shown that cord blood–derived $CD14^+$ monocytes improve brain function and modulate brain inflammation through a paracrine mechanism (Saha et al. 2019). $CD14^+$ monocytes have also been demonstrated to be responsible for brain remyelination, increased brain connectivity, stimulation of oligodendrocyte proliferation, and modulation of neuroinflammation (Saha et al. 2019). A study by Terry et al. showed that $CD34^+$/M-cadherin$^+$ cells from BM could release proangiogenic cytokines and growth factors and differentiate into vascular cells, contributing to microvascular remodeling (Terry et al. 2011). Li et al. demonstrated that $CD117^+$ cells generated VEGF and differentiated into endothelial cells (ECs), facilitating increased microvessel density and blood perfusion in mice (Li et al. 2003). Previous studies have shown that BM-derived $CD133^+$ cells improve endothelial function (Hristov and Weber 2008), ischemia, and bone generation (Li 2013). $CXCR4^+CD45^-$ BMMNCs have been reported to reduce infarction volume and neurologic deficits, decrease TNF-α levels and increase VEGF in the brains of ischemic stroke mouse models (Wang et al. 2015). MSCs have been shown to provide anti-inflammatory and neuroprotective effects, enhance angiogenesis and neurogenesis, and improve function (Andrzejewska et al. 2021; Hoang et al. 2022). It is believed that interactions among various BMMNC cell types are also important in certain diseases. The interaction between cell types among BMMNCs might result in additive, synergistic, or even detrimental effects on the efficacy of cell therapies. Recently, Yang et al. reported that myeloid cell lineage and stem cell/progenitor cells appear to be key components among BMMNCs that improve functional and histological outcomes in mice after stroke (Yang et al. 2016). However, the specific myeloid cell types and stem/progenitor cells that are important have not yet been identified. Further studies are needed to address this question. Depleting specific cell types using antibodies or utilizing animals with knockout and/or deficiency of certain genes could be helpful in studying the role of each cell population among BMMNCs.

Paracrine Effects

The paracrine effects of BMMNCs are emerging as an important mechanism in regenerative medicine. Studies have shown that BMMNCs can increase angiogenesis and anti-inflammatory effects and provide neuroprotection in neurological diseases (Fig. 1).

Angiogenesis

During angiogenesis, new vessels are formed from preexisting vessels through nonsprouting and sprouting mechanisms, together with an increase in interaction among pericytes, ECs and smooth muscle cells to create a vascular network (Zadeh and Guha 2003). The administration of BMMNCs has been demonstrated to induce angiogenesis via various mechanisms of action (Fig. 2). Vascular endothelial growth factor (VEGF) is one of the main regulators of angiogenesis (Uccelli et al. 2019). Evidence suggests that EPCs promote angiogenesis to improve neurological outcomes by increasing VEGF levels (Asahara et al. 1997). Li et al. demonstrated that $CD117^+$ cells generated VEGF, contributing to increased microvessel density and blood perfusion in mice (Li et al. 2003). $CXCR4^+CD45^-$ BMMNCs have been reported to increase VEGF levels in the brains of ischemic stroke mouse models (Wang et al. 2015). Overall, these studies reported that VEGF can be increased by BMMNCs.

Pericytes are known to play a crucial role in vessel growth and maturation, and VEGF has been demonstrated to induce pericyte recruitment and the subsequent release of angiopoietin-1 (Ang-1), a key molecule involved in stabilizing blood vessels and promoting vessel maturation (Stratman et al. 2009; Hellström et al. 2001).

A study by Terry et al. revealed that $CD34^+$/M-cadherin$^+$ cells from BM could release proangiogenic cytokines and growth factors contributing to microvascular remodeling (Terry et al. 2011). CXCL-10 has been found to stimulate the migration and recruitment of MSCs (Kalwitz et al. 2010). The study showed that the stimulatory cytokine CXCL-10 was significantly increased by $CD34^+$/M-cad$^+$ cells. A significant release of CXCL-10 by $CD34^+$/M-cad$^+$ cells may help recruit endogenous MSCs from the BM to assist in the restoration of blood flow and synergize with cytokines to promote arteriogenesis (Terry et al. 2011). The administration of BMMNCs significantly increased the density of microvessels and the expression of angiogenic factors, including VEGF, basic fibroblast growth factor (FGF), and Ang-1 (Jeon et al. 2007). Reportedly, BMMNC administration can increase the neovascularization of ischemic tissue by depositing EPCs into the vasculature (Park et al. 2011). These cells replace injured mature ECs by incorporating into blood vessels, and they secrete many proangiogenic factors to promote the survival and proliferation of ECs (Urbich et al. 2003). Majka et al. (2001) demonstrated that numerous angiogenic factors, such as VEGF, hepatocyte growth factor (HGF), FGF-2, TGF-β1, as well as cytokines and chemokines involved in angiogenesis, including IL-8, MCP-1, and MIP-1α, were detected in media cultures of normal BM-derived $CD34^+$ cells (Majka et al. 2001). A recent study by Kikuchi-Taura et al. found that BMMNCs activated angiogenesis via gap junction-mediated cell–cell interactions in which BMMNCs induced VEGF uptake into ECs by increasing the expression and activation of hypoxia-inducible factor-1α (HIF-1α). Activation of HIF-1α enhanced the phosphorylation of endothelial nitric oxide synthase (eNOS), which is a key mechanism of cell therapy–mediated angiogenesis (Kikuchi-Taura et al. 2020). Autophagy is known to be induced by a deficient energy supply in ischemic tissue, and glucose is the major energy source in ECs (Keaney and Campbell 2015). By transferring glucose to ECs, BMMNCs suppressed autophagy in the cells (Kikuchi-Taura et al. 2020).

Neuroprotection

The neuroprotective effects of BMMNCs have been demonstrated in previous studies (Fig. 3). BMMNCs decreased soluble intercellular adhesion molecule-1 (ICAM-1) and increased the serum level of VEGF, leading to a reduction in neuropathic symptoms, including foot pain, numbness, and weakness, after administration in patients with refractory diabetic sensorimotor polyneuropathy (Wei et al. 2020). Supernatants of BMMNC cultures containing trophic factors, such as insulin-like growth factor (IGF), VEGF, and stromal cell-derived factor-1 (SDF-1), provided neuroprotection against oxygen–glucose deprivation and hypoxia and reduced neuronal death, oxidative stress, and microglial and macrophage-mediated toxicity in ischemic stroke (Sharma et al. 2010).

Previous reports have demonstrated that BM-derived stem cells release neurotrophic factors, including nerve growth factor (NGF), neurotrophin-3 (NT-3), glial cell line–derived neurotrophic factor (GDNF), fibroblast growth factor-2 (FGF-2), and IGF-1, which play important roles in neurogenesis (Boucherie et al. 2008; Crisostomo et al. 2008; Pisati et al. 2007). MSCs from BM also secrete brain-derived neurotrophic factor (BDNF), a potentially neuroprotective growth factor that plays a vital role in improving neuronal survival by protecting neurons from trophic deprivation and nitric oxide–induced death (Wilkins et al. 2009). BM-derived monocytes migrate to the central nervous system (CNS), where they exert neuroprotective effects, increase brain connectivity, and stimulate oligodendrocytes (Lampron et al. 2013; Herz et al. 2017; Saha et al. 2019). In addition, BMMNC administration elevated HGF levels in CSF in a rat model (Yoshihara et al. 2007) and a dog model (Tamura and Maeta 2020) of SCI and exerted neuroprotective effects by introducing many growth factor–producing cells, facilitating hindlimb locomotor function in a rat model of SCI (Arai et al. 2016).

The protease caspase-3 plays a crucial role in ischemic neuronal apoptosis. Sharma et al. reported that medium from BMMNC cultures prevented caspase-3 activation and neuronal death in vitro (Sharma et al. 2010). The administration of BMMNCs reduced the number of apoptotic cells at the site of injury in the spinal cord (Arai et al. 2016). EPCs overexpress Bcl-2, an anti-apoptotic factor in brain tissue, suggesting that EPCs play an anti- apoptotic role, contributing to improved outcomes after cell infusion (Hong et al. 2020).

Anti-inflammatory Effects

BMMNCs exert anti-inflammatory effects by secreting or inhibiting several cytokines. Using a mouse model, Takamura et al. showed that intrathecal administration of BMMNCs suppressed the migration and accumulation of microglia and reduced the expression of inflammatory cytokines (IL-6, IL-1β, and TNF-α) in the CSF, resulting in the relief of neuropathic pain after spinal nerve injury in mice (Takamura et al. 2020). Wang et al. demonstrated that the $CXCR4^+CD45^-$BMMNC subpopulation reduced TNF-α expression in the brains of an ischemic mouse model (Wang

Table 8 The roles of BMMNC subtypes in the treatment of neurological diseases

Cell type	Main findings	References
EPCs	– Participate in blood vessel formation – Vascular repair and remodeling – Promote angiogenesis through the release of VEGF, EC proliferation – Increase vascular diameter and the number of branch points in ischemic regions in a cerebral ischemic animal model – Anti-apoptosis	Kong et al. (2018), Hong et al. (2020), Asahara et al. (1997)
MSCs	– Anti-inflammatory effects – Reduce lesion size, cell death – Neuroprotection – Enhancement in neurogenesis – Functional improvement – Maintenance and remodeling of axons – Remyelination – Disease symptom amelioration	Andrzejewska et al. (2021), Hoang et al. (2022)
HSCs ($CD34^+$)	– Induction of migration – Induction of angiogenesis – Modulation of neuroinflammation – Differentiation into ECs	Saha et al. (2019)
$CD34^+$/M-cadherin$^+$ cells	– Promote arteriogenesis and angiogenesis	Terry et al. (2011)
$CD117^+$ cells	– Increase microvessel density and blood perfusion, endothelial differentiation, VEGF release	Li et al. (2003)
$CXCR4^+CD45^-$ cells	– Enhance VEGF expression – Reduce infarction volume and neurological deficits – Decrease TNF-α expression in the brain of ischemic stroke mouse models	Wang et al. (2015)
$CD133^+$ cells	– Improve endothelial function, ischemia, and bone generation	Li (2013), Hristov and Weber (2008)
Monocyte	– Migrate to CNS and remain confined to the sites of injury – Neuroprotective effects	Lampron et al. (2013), Herz et al. (2017)
Muse cells	– Migrate to the spinal cord, supporting motor neuron survival and suppressing myofiber atrophy – Differentiate into astrocyte-lineage cells or neural cells, facilitating neural reconstruction and function	Kajitani et al. (2021), Uchida et al. (2017), Yamashita et al. (2020)

EPCs endothelial progenitor cells; *ECs* endothelial cells; *HSCs* hematopoietic stem cells; *MSCs* mesenchymal stromal/stem cells; *CD* cluster of differentiation; *CXCR* C-X-C chemokine receptor; *VEGF* vascular endothelial growth factor; *TNF-α* tumor necrosis factor; *CNS* central nervous system

et al. 2015). A reduction in TNF-α after BMMNC administration was also observed in a rat model of ischemic stroke (Suda et al. 2014) and in patients with refractory diabetic sensorimotor polyneuropathy (Wei et al. 2020). In addition, BMMNC infusion increased anti-inflammatory cytokines (IL-4 and IL-10) in epileptic rats (Costa-Ferro et al. 2012). Bedi et al. demonstrated that BMMNC administration preserved BBB integrity, attenuated the activated microglial/macrophage response, and improved cognitive function in a controlled cortical impact rodent model of TBI(Bedi et al. 2013).

Modulation of Systemic Inflammation

Altered communication between the central nervous system and immune cells contributes to the pathology of several neurological and psychiatric disorders (Dantzer 2018; Matejuk et al. 2021). In an animal model of chronic mild stress, BMMNCs reversed the upregulation of HMGB-1, which is a key factor in initiating neuroinflammation and depressive behaviors (Wang et al. 2018; Zhang et al. 2019), and increased the levels of the neurogenic factor BDNF in the hippocampus and spleen (Costa-Ferro et al. 2022). Furthermore, cell therapy suppressed IL-1β expression in the tissue of the former structure, which further accelerated its anti-inflammatory effect. As a result, mice transplanted with BMMNCs demonstrated superior resistance to

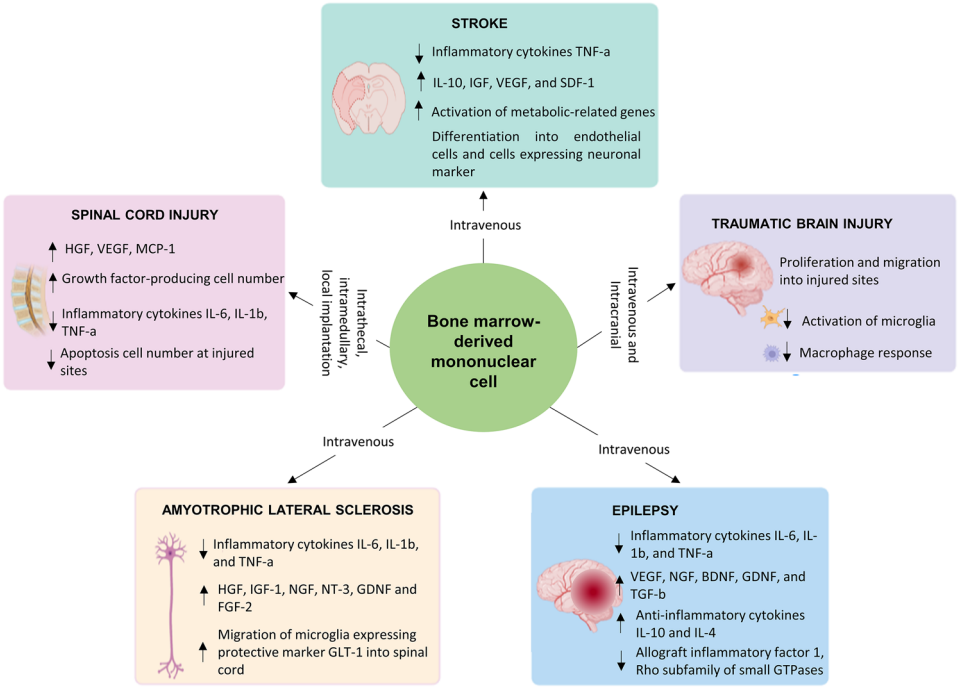


Fig. 1 Paracrine effects of BMMNCs in animal models of different neurological diseases**.** In stroke, BMMNCs reduce the levels of inflammatory cytokines, such as TNF-α; increase the levels of growth factors and the anti-inflammatory cytokine IL-10; activate metabolism-related genes; and differentiate into ECs and cells expressing the neuronal marker NeuN. In SCI, BMMNCs also induce the production of growth factors, increase the number of growth factor–producing cells, and reduce inflammatory cytokine levels and cell apoptosis in the injured spinal cord. In TBI, BMMNCs might proliferate and migrate to injured sites to attenuate microglial activation and reduce macrophage responses. In ALS, BMMNCs decrease inflammatory cytokines and increase neurotrophic factors and growth factors. BMMNCs also migrate to the spinal cord and express the neuroprotection marker glutamate transporter-1. In epilepsy, BMMNCs suppress inflammatory cytokines, increase anti-inflammatory cytokines and growth factors, and decrease allograft inflammatory factor-1 and the Rho subfamily of small GTPases

stress-induced depression (Costa-Ferro et al. 2022). In line with these observations, BMMNCs counteracted the secretion of proinflammatory factors, including TNF-α, IL-6, and histone H3, and thus reduced systemic inflammation and endothelial tissue damage in sepsis (Matsubara et al. 2021). MSCs, NSCs, and multipotent adult progenitor cells in the BM exhibit significant immunomodulatory properties (Corey et al. 2020; Stonesifer et al. 2017). These cells activated T regulatory cells; modulated the cytokine landscape by reducing inflammatory IL-1β, IL-6, MCP-1, and MIP-1α while increasing anti-inflammatory IL-4, IL-10, and TNF-β; and reduced microglial activation in ischemic stroke (Huang et al. 2014; McGuckin et al. 2013; Chen et al. 2013).

It remains unclear whether migration of BMMNCs to the brain is necessary for their therapeutic effects. In addition to the brain, BM-MSCs also migrate to other organs, including the lung, liver, spleen, and kidney, in chronic stroke (Yang et al. 2011; Acosta et al. 2015). The importance of the spleen in the pathology of stroke has been demonstrated in several studies, in which animal models of brain injury concurrently exhibited undersized spleens with reduced numbers of CD8+ T cells (Yang et al. 2017; Vendrame et al. 2006). Acosta et al. revealed better survival of BM-MSCs in the spleen than in the brain, with 0.03% and 0.0007% survival, respectively. Despite the very low rates of homing, BM-MSCs significantly abrogated neuroinflammation, reduced neural loss, and improved motor and cognitive deficits in animal stroke models (Acosta et al. 2015). Interestingly, BM-MSCs and umbilical cord blood cells were able to migrate from the cerebrum to the periphery via the lymphatic system to modulate the inflammatory response in the spleen (Vendrame et al. 2004; Xu et al. 2019). This behavior seemed to be a prerequisite for the neuroprotective effects mediated by human multipotent adult progenitor cells, as splenectomized animals failed to benefit from cell therapy (Yang et al. 2017). Accordingly, the therapeutic effect of BM-MSCs was correlated with their presence in the spleen and inversely depended on the systemic inflammation status (Acosta et al. 2015).

Homing and Differentiation

In vitro experiments and animal studies have revealed that BMMNCs can migrate to target sites, including abnormal

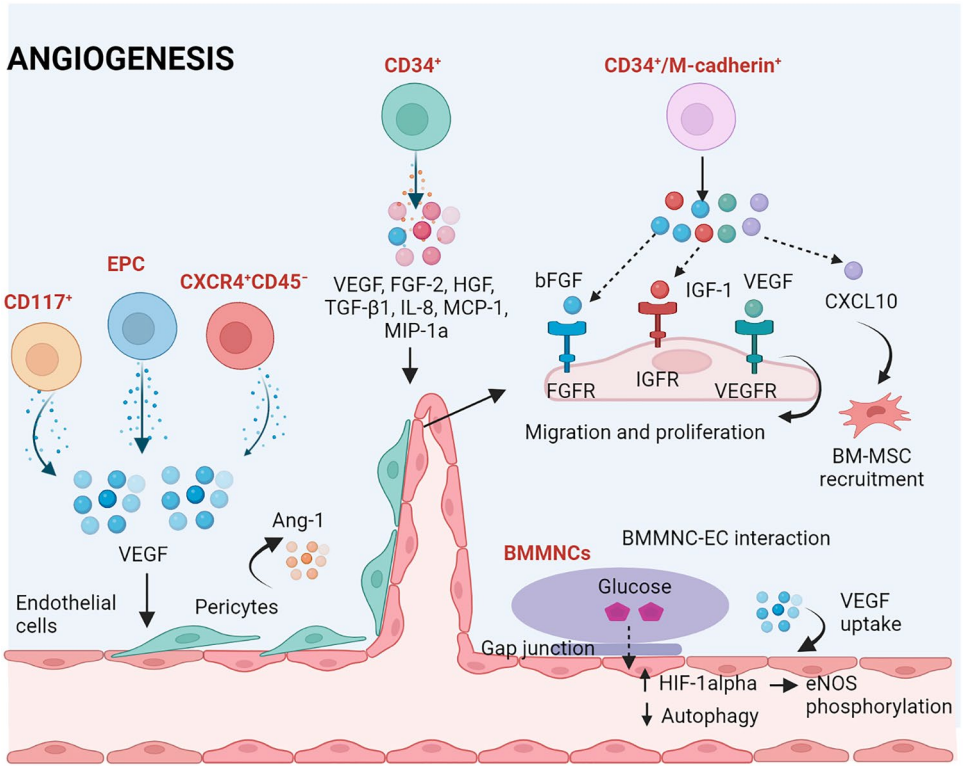


Fig. 2 BMMNCs induce angiogenesis. BMMNCs ($CD34^+$, $CD117^+$, $CXCR4^+CD45^-$ cells) secrete VEGF, promoting pericyte detachment from ECs for endothelial sprouting, and pericytes release Ang-1 for vessel growth and maturation. VEGF, basic FGF (bFGF), and IGF produced by CD34+/M-cadherin + BMMNCs stimulate the migration and proliferation of ECs. CXCR10 secreted by $CD34^+$/M-$cadherin^+$ cells recruits BM-derived mesenchymal stem/stromal cells (BM-MSCs) to the target site. $CD34^+$ cells release angiogenic factors (VEGF, HGF, FGF-2, and TGF-β1), cytokines, and chemokines (IL-8, MCP-1, and MIP-1α) involved in angiogenesis. Interaction between BMMNCs and ECs results in glucose transfer from BMMNCs into ECs for energy supply, VEGF uptake by ECs via gap junctions between the cells, increased expression and activation of HIF-1α, enhanced eNOS phosphorylation, and decreased autophagy of ECs

brain areas (Sohni and Verfaillie 2013). Hematopoietic cells from BM migrated to the brains of mice three days after administration and were widely distributed throughout the brain, including the hippocampus, brain stem, thalamus, cortex, and cerebellum (Eglitis and Mezey 1997). $CD34^+$ cells have been demonstrated to migrate to sites of injury in patients with chronic SCI to restore damaged neuronal cells (Callera et al. 2007) (Fig. 4).

The differentiation capacity of BMMNCs is still a matter of ongoing research and debate (Fig. 4). Studies have illustrated that stem cells from BM can differentiate into ECs in situ (Jackson et al. 2001). Li et al. demonstrated that $CD117^+$ cells differentiated into ECs, facilitating increased microvessel density and blood perfusion in mice (Li et al. 2003). Carneiro et al. reported that BMMNCs from C57BL/6 mice cultured in different conditions differentiated into early EPCs capable of differentiation into major ECs to participate in the re-endothelization of damaged vessels (Carneiro et al. 2015). Early studies provided evidence that stem cells from BM can differentiate into neural and glial cells (in vitro and in vivo (Darabi et al. 2013; Song et al. 2007), microglia and astrocytes in the brains of recipient mice (Eglitis and Mezey 1997), vascular cells(Terry et al. 2011), oligodendrocytes (Akiyama et al. 2002), and cells expressing the neuronal marker NeuN [in the brains of recipient mice (Mezey et al. 2000b) and in the CNS of adult mice(Brazelton et al. 2000)]. However, several studies have shown that the BM cells were not transdifferentiating through their intrinsic transdifferentiation capacity. Studies have reported that the transdifferentiation may be due to cell fusion. Tetara et al. demonstrated that BM cells could spontaneously fuse with a variety of different cell types, including hepatocytes, myocytes, and neurons, leading to the expression of markers of the fused cells in the BM cells (Terada et al. 2002). Another study by Alvarez Dolado et al. showed that BM cells from male mice were able to fuse with Purkinje neurons, cardiomyocytes, and hepatocytes in female mice, leading to the expression of male-specific genes in the fused cells. This suggests that fusion may be a mechanism by which BM cells can adopt characteristics

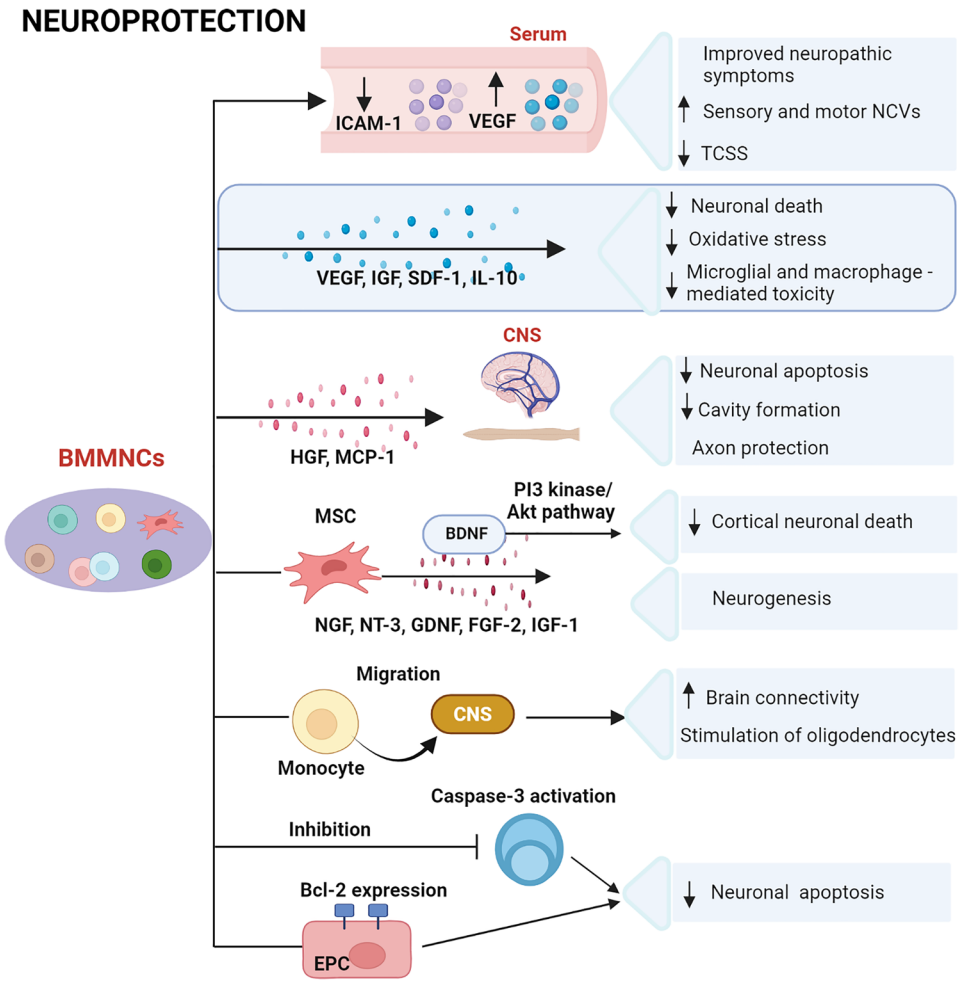


Fig. 3 Neuroprotective effects of BMMNCs. BMMNCs improve neuropathic symptoms, increase sensory and motor nerve conduction velocity (NCV), and decrease Toronto Clinical Scoring System (TCSS) scores by decreasing ICAM-1 and increasing VEGF. BMMNCs release neurotrophic factors (VEGF, IGF, SDF-1, IL-10, HGF, MCP-1, NGF, NT-3, GDNF, FGF-2, and IGF-1) to reduce neuronal death, oxidative stress, microglial and macrophage-mediated toxicity, and cavity formation and provide axon protection and neurogenesis. BM-derived monocytes migrate to the CNS to increase brain connectivity and stimulate oligodendrocytes. BMMNCs inhibit caspase-3 activation and enhance the expression of Bcl-1 on EPCs to reduce apoptosis

of different cell types (Alvarez-Dolado et al. 2003). Cell fusion has also been demonstrated to be the principal source of BM–derived hepatocytes (Wang et al. 2003; Vassilopoulos et al. 2003; Alvarez-Dolado et al. 2003). In addition, some researchers suggest that the observed differentiation into neural cells may be due to contamination with neural precursor cells rather than transdifferentiation of BMMNCs themselves. Sanchez-Ramos et al. showed that BM stromal cells from adult rats could differentiate into cells with neuronal morphology and express neural markers in vitro. However, the authors acknowledged that the possibility of contamination with neural precursor cells could not be ruled out as a cause of the observed results (Sanchez-Ramos et al. 2000). A study by Bjornson and colleagues reported that BM cells from male mice could give rise to cells bearing neuronal antigens in the brains of female mice that had been irradiated and then received BM transplants. However, the authors noted that contamination with neural precursor cells from the donor mice could not be ruled out as an explanation for the observed results (Mezey et al. 2000a). Contamination with neural crest–derived stem cells and tissue culture artifacts is suggested to be a mechanism contributing to the apparent switch to a neural phenotype in MSCs (Somoza et al. 2008; Montzka et al. 2009).

In general, BMMNCs can migrate and home to affected sites. However, the differentiation capacity of BMMNCs is still an area of active research, and more studies are needed to fully understand their potential. Furthermore, stem cells make up a very small percentage of BMMNCs, and even if the BMMNC transdifferentiation occurs, the low number of BMMNCs that reach the CNS, differentiate into neural cells, survive, and integrate into neural tissue implies that this process might not be the main protective mechanism of BMMNCs.

Mitochondrial Transfer

Mitochondria play an essential role in energy metabolism and are crucial for various cellular activities. They provide the energy necessary to drive the physiological functions of cells. Mitochondrial dysfunction has been identified in neurological disorders (Norat et al. 2020). Recently, more

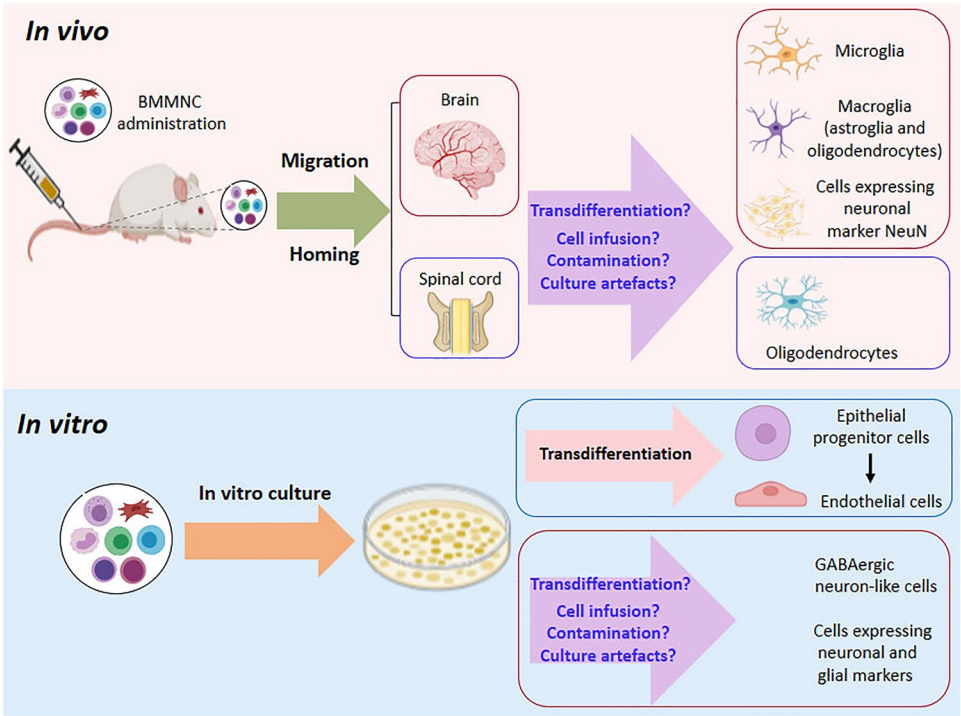


Fig. 4 Migration and differentiation potential of BMMNCs in vitro and in vivo. Intravenously infused BMMNCs migrate to the mouse brain and spinal cord. Those that reach affected brain areas express markers of microglia or macroglia (astroglia and oligodendrocytes) or the neuronal marker NeuN, and those that reach the injured spinal cord express markers of oligodendrocytes. However, further research must explore whether BMMNCs can differentiate into cells or whether other mechanisms, such as cell infusion, contamination, or culture artifacts, are involved. In vitro, under different culture conditions, BMMNCs can differentiate into EPCs, ECs, gamma-aminobutyric acid-secreting (GABAergic) neuron-like cells, and cells expressing neuronal and glial markers

evidence has demonstrated that mitochondrial transfer between cells can rescue and revitalize exhausted cells. Hayakawa et al. reported that EPC-derived extracellular mitochondria can be incorporated into normal brain ECs to support brain endothelial energetics, barrier integrity, and angiogenic function (Hayakawa et al. 2018). Mitochondrial transfer from BM-MSCs to motor neurons in SCI rats reduced apoptosis during the early stage of SCI, improved the recovery of locomotor function, and decreased the size of the lesion cavity and glial scar during the late stage of SCI (Li et al. 2019). Liu et al. demonstrated that BM-MSC mitochondria transferred to ECs and provided protective effects by improving the mitochondrial activity of damaged microvessels, enhancing angiogenesis, and reducing infarct volume in an ischemic stroke rat model (Liu et al. 2019). Tunneling nanotubes, extracellular vesicles, gap junctions, uptake of isolated mitochondria, and cell fusion have been considered among the possible mechanisms of mitochondrial transfer (Tan et al. 2022).

Extracellular Vesicles

Cells in the central nervous system orchestrate a complex communication network to maintain their neural circuits in health and diseases (Ruan et al. 2021). In addition to the paracrine effects of soluble factors, extracellular vesicles (EVs) provide a unique mechanism governing intercellular interactions. EVs contain numerous messenger molecules in the form of proteins, mRNAs, microRNAs, long noncoding RNAs, metabolites, lipids, and even mitochondria to target cells (Ruan et al. 2021; Tan et al. 2022). Furthermore, EVs can permeate the BBB, which makes them more capable of reaching the brain than cellular drugs (Ramos-Zaldívar et al. 2022). Although the majority of EVs are trapped in the liver, spleen, lung, pancreas, and GI tract, ca. One percent of injected EVs reach the brain (Wiklander et al. 2015). Macrophage-derived EVs express the integrin lymphocyte-function-associated antigen 1, which interacts with ICAM-1 on ECs to mediate entry into the brain parenchyma. This is further enhanced in response to inflammation (Matsumoto et al. 2017; Yuan et al. 2017). In vitro data and experiments in zebrafish suggested that EVs crossed the BBB via transcytosis, a process mediating the transport of macromolecules from one side of a cell to the other through a cellular barrier (Ramos-Zaldívar et al. 2022).

BM-MSCs in the BM microenvironment are the most frequently reported source of EVs with therapeutic applications in neurological diseases (Ghafouri-Fard et al. 2021; Gautheron et al. 2023). EVs secreted by BM-MSCs have exhibited immunosuppressive, neurogenic, and proangiogenic properties (Reed and Escayg 2021; Yuan et al. 2022). Similar to BM-MSCs, their EVs produced an anti-inflammatory milieu with a decrease in IL-1α, IL-1β, and IL-6 and an increase in IL-10 in rodent models of stroke and TBI

(Kim et al. 2016; Dabrowska et al. 2019). This resulted in the deactivation of immune cells and astrocytes in ischemic regions (Dabrowska et al. 2019). Exosomes polarize activated helper T cells into regulatory T cells (Zhang et al. 2014) while polarizing proinflammatory M1 microglia into the anti-inflammatory M2 phenotype via the ERK1/2 pathway (Zhao et al. 2020). Furthermore, neurogenesis was significantly stimulated in the presence of BM-MSC-derived EVs. Axonal and synaptic density were increased along the ischemic boundary zone of the cortex and striatum in treated mice, which were subjected to middle cerebral artery occlusion to induce stroke (Xin et al. 2013). EVs contain many factors that stimulate axon growth, regeneration of oligodendrocytes, and remyelination, leading to white matter recovery after stroke (Otero-Ortega et al. 2017). In an experimental TBI model, exosomes positively impacted immature and mature neurons in the dentate gyrus (Zhang et al. 2015). They reduced glutamate levels and the expression of GLT-1, a presynaptic glutamate transporter, via downregulation of p38 MAPK signaling in astrocytes. Consequently, caspase-3 and cleaved caspase-9 levels marking apoptotic neurons were reduced in exosome-treated TBI rats (Zhuang et al. 2022). In these models, neurogenesis was often accompanied by angiogenesis. Indeed, EVs enhanced the formation of new blood vessels in ischemic regions of experimental stroke (Doeppner et al. 2015). Similarly, exosomes induced proliferation of ECs in the lesion region and dentate gyrus of TBI mice to further stimulate neural regeneration (Zhang et al. 2015). In Alzheimer's disease, neprilysin, an endopeptidase found in BM-MSC-derived EVs, was capable of digesting Aβ plaques and reversing cognitive impairment induced by beta amyloid 1–42 (Reza-Zaldivar et al. 2019; Elia et al. 2019). Overall, EVs are a powerful tool for cell−cell communication. The functions of EVs secreted by other BMMNC populations outside BM-MSCs remain elusive.

Other Mechanisms

In a recent study, it was reported that BM-derived microglia could be recruited to the CNS and phagocytose amyloid β accumulated in Alzheimer's disease (Li et al. 2020). Ogawa et al. (2021) reported that BMMNC administration activated metabolism-related genes in the contralateral cortex at 3 h after BMMNC administration and improved motor function at 10 weeks after cell therapy in a murine stroke model(Ogawa et al. 2021).

Taken together, these findings show that BMMNCs mainly act via mechanisms such as homing; differentiation; and paracrine effects, including angiogenesis, neuroprotection, and anti-inflammatory effects. The potential outcomes of BMMNCs in the treatment of neurological diseases are probably due to these mechanisms.

Indications for BMMNC Administration to Treat Neurological Diseases

For decades, BMMNCs have been employed in numerous clinical trials and therapeutic services in the treatment of several diseases. However, good results are not achieved in all patients after treatment. This issue raises the question of when BMMNC administration should be indicated. Nguyen et al. demonstrated that clinical improvements were observed in patients with ASD of different degrees of severity after BMMNC transplantation, while ASD patients with severe genetic alterations related to the disease showed no responses to the treatment, suggesting that genetic changes might have an impact on the outcomes of BMMNC therapy (Nguyen Thanh et al. 2021). While several studies employed BMMNCs in treating CP without referring to its causes (Sharma et al. 2012; Liu et al. 2017). Liem et al. infused the cells in selected patients with CP due to acquired causes, such as neonatal icterus or oxygen deprivation, but not in patients with CP due to congenital causes related to genetic abnormalities (Liem et al. 2017; Nguyen et al. 2018; Thanh et al. 2019). Thus, indications for BMMNC administration in treating neurological diseases should be based on the etiology, and we suggest that BMMNC administration should be indicated only for patients without genetic abnormalities.

In addition, the stage, extent, phase (acute, subacute, or chronic conditions), and chronicity as well as the age of treated patients might also influence the effectiveness of BMMNC therapy. A study by Sharma et al. showed that SCI patients for whom intervention was performed early (12 months postinjury) or those who were younger (under 18 years old) achieved better functional outcomes of BMMNC treatment (Sharma et al. 2020b). The same team also showed that the percentages of improvement in FIM scores of patients gradually decreased from patients with American Spinal Injury Association (ASIA) grade A SCI to patients with ASIA grade D SCI, indicating that the rate of improvement was inversely proportional to the severity of the injury (Sharma et al. 2020b). Therefore, BMMNC administration should be performed at early stages of disease to achieve the best outcomes.

Advantages and Limitations of the Application of BMMNCs for Neurological Diseases

BMMNCs have been used in clinical trials for the treatment of several neurological diseases, with promising outcomes thus far. BMMNCs have several advantages over

other types of stem cells. BMMNCs can be easily isolated from BM aspirates using an inexpensive method, density gradient centrifugation. While other cell types require time for culture/expansion, BMMNCs can be used in patients immediately after being harvested. Therefore, BMMNCs can be used early in treatment, which can be advantageous for patients because diseases may worsen over time or even during the preparation of other cell types. In addition, because BMMNCs do not require cultivation, the cost of BMMNC therapy can be less than that of cell therapies that require intensive preparations and cultures. Furthermore, the risk of malignant transformation occurring during long-term in vitro cell culture (Taguchi et al. 2015b) can be eliminated when BMMNC therapy is used.

However, the use of BMMNCs still has many challenges and limitations that need to be resolved. The first limitation of BMMNC application is that the optimal dose, number of injections, and delivery route for each neurological disease have not yet been established. Most clinical trials to date have administered all harvested BMMNCs without determining an optimal dose. This issue of unknown optimal cell counts obviously leads to difficulties in validating and quantifying the outcomes of BMMNC administration. Another limitation is that BMMNCs include different subtypes, whose individual roles have not yet been fully studied. Moreover, the interactions among subtypes in BMMNCs that might result in additive, synergistic, or even detrimental effects on the efficacy of cell therapies should be further investigated to enhance the effectiveness of BMMNC administration.

Several factors influence the quality of BMMNCs. A previous study demonstrated that the neuroprotective effects of BMMNCs in vitro were dependent on age in an experimental stroke model (Wagner et al. 2012). Aging has also been reported to impair angiogenic capacity (Zhuo et al. 2010) and hamper the neovascularization (Sugihara et al. 2007) of sites containing BMMNCs. Nguyen et al. showed that alterations in the mitochondrial DNA of BM-derived MSCs affected the proliferation and metabolism of cells, consequently altering the outcomes of autologous cell administration (Nguyen et al. 2021). They suggested that autologous administration of BM-derived MSCs for the treatment of type 2 diabetes mellitus should be performed specifically in nonobese patients with a disease duration under 10 years (Nguyen et al. 2021). Thus, age and comorbidities should be considered when evaluating the efficacy of BMMNC administration for neurological diseases.

Due to rejection issues, BMMNCs have mainly been administered to patients autologously thus far. The number of participants enrolled in the clinical trials is limited, and many studies to date have been case report studies. The lack of control groups has it difficult to draw an accurate conclusion about the effects of a single BMMNC administration. Therefore, further randomized controlled clinical trials employing larger sample sizes should be performed to obtain better insight into the role of BMMNCs in the treatment of neurological diseases.

Conclusion

In this review, we discussed the known and unknown aspects of BMMNC applications in the treatment of neurological diseases. We suggest the following:

(1) For the administration of BMMNCs to treat neurological diseases, the intrathecal route is ideal because it is minimally invasive while maximizing the number of infused cells reaching the target areas.
(2) The proper volume of BM should be aspirated to ensure that positive effects are achieved without impairing the patient's hemodynamics. Accordingly, further studies are also needed to determine the optimal number of injections for each neurological disease. The relationship among the administration routes, doses, and outcomes of BMMNC-based therapies is a question that remains to be answered through further investigation.
(3) The proposed mechanisms of BMMNCs include angiogenesis, homing, differentiation, paracrine signaling and anti-inflammatory effects. Other potential mechanisms linking BMMNCs to treatment outcomes should be further explored using animal models, as should the roles of various BMMNC subtypes.
(4) Autologous BMMNC administration should be indicated after careful consideration of the genetic abnormalities involved and the stage of disease.
(5) Additional randomized clinical trials should be performed to draw accurate conclusions about the efficacy of BMMNCs in the treatment of neurological conditions.

Although BMMNC administration has led to improvements in the treatment of several different neurological diseases, there are still challenging questions that need to be answered through preclinical and clinical trials to enhance the effectiveness of BMMNC therapy in the future.

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