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Invited Review

Position statement from the Advocacy Committee of the ICNA On Stem Cell Therapies in Autism Spectrum Disorders and Cerebral Palsy

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Background

Despite marked advances in the field, curative treatments for neurodevelopmental disorders are still lacking. Treatment is primarily symptomatic and often limited in efficacy. Often desperate for a cure, caregivers of children with these conditions are vulnerable to the promise of treatments with limited evidence, such as stem cell therapy (SCT). In recent years, despite SCT being in early research stages to determine what, if any, role it may have in the treatment of neurodevelopmental conditions such as autism spectrum disorder (ASD) and cerebral palsy (CP), some centres around the world are now offering this intervention with unclear risks and unproven benefits, at high cost, posing a concern for clinicians managing these children.

Autism Spectrum disorder (ASD) is a heterogeneous and complex neurodevelopmental disorder characterized by persistent deficits in social communication, language, and interaction, and restricted, repetitive patterns of behaviour, interests, or activities. There is a wide variation in symptoms, intellectual function, severity, and functional disability [1]. The exact cause and pathophysiology of ASD are unknown, with several mechanisms possibly involved, including genetic factors, environmental factors, chronic neuroinflammation, mitochondrial dysfunction, oxidative stress, immune dysregulation, and hormonal imbalance [2]. Management of ASD is typically symptom-driven, with a combination of pharmacologic therapies (such as psychotropic drugs) used at times to manage the associated behaviour issues, and typical interventions including early intensive behavioural therapy, applied behaviour analysis, occupational therapy, social skills training and speech therapy [3, 4]. Despite the absence of a common causal pathway and its multifactorial nature, there is ongoing research on the feasibility of novel disease-modifying therapies, such as gene therapy and SCT, for ASD. SCT is based on the hypothesized contribution of inflammatory and immune dysregulation in ASD [5].

CP is a diagnosis based on the clinical presentation of a neuromotor impairment due to a non-progressive injury to the developing brain (typically defined as the first two years of life) [6]. Cerebral palsy (CP) can be caused by a multitude of aetiologies that result in injury to the developing brain and is classified in multiple ways, including motor impairment type, topographical distribution, and severity. Genetic etiologies may, in some instances, contribute to the final causal pathway resulting in CP; however, this remains under investigation. Treatment is focused on preventing the occurrence and therapeutic interventions when it occurs. Curative treatments are absent, and like ASD, caregivers often utilize a wide range of complementary therapies de-

spite minimal evidence supporting such use, as standard treatments are limited in effectiveness. SCT is also being studied for potential utility in CP based on the theorized actions of cellular repair and anti-inflammatory mechanisms. However, evidence for this treatment remains limited to date.

In both ASD and CP, the heterogeneity of the conditions poses a challenge in clinical treatment trials, specifically the absence of clear objective markers for improvement and identifying a reasonable target for a cure. Thus, while there are small studies evaluating the potential benefits of SCT in both conditions, evidence remains very limited, and its utility in clinical care still needs to be discovered.

What are stem cells?

Stem cells are primitive cells that can regenerate, divide and produce. They specialize and differentiate to form specific cells. There are various types of stem cells. The embryonic stem cells are derived from embryos three to five days old and can differentiate to form all types of cells and tissues of the body; therefore, they are "pluripotent". However, to obtain these stem cells, embryos need to be sacrificed. There are various extraembryonic sources of stem cells, such as those derived from bone marrow, umbilical cord, placenta, neural tissues, and the foetus, namely human pluripotent stem cells (hPSC). Their capacity to regenerate and differentiate varies. Most of them are not as versatile and durable as embryonic stem cells, and they cannot differentiate into all cell types [7, 8, 9].

The recent technology of developing induced pluripotent stem cells (iPSCs) is a breakthrough that obviates the need for sacrificing embryos. The iPSCs derived from different methods have similar characteristics to embryonic stem cells. They can self-renew, express stem cell markers, and differentiate into the cell of all three germ layers except cells in extraembryonic tissue [5]. Recently, iPSC researchers have suggested a role for hPSC in ASD, and that iPSC could become an alternate option [9]. The report notably highlighted issues that included (*i*) sources of variance, (*ii*) scale and format of study design, (*iii*) divergence from the human brain in vivo, and (*iv*) regulatory policies and compliance governing the use of hPSCs [9].

What is the available evidence of the efficacy of stem cell therapy in ASD and CP?

Several ASD animal models have been developed, and some benefit has been documented using stem cells [10]; however, none are perfectly suitable and represent the disorder in human beings. Hence it is difficult to extrapolate the effect of these therapies on humans. Some basic animal models for CP also exist, as well as some potentially promising data for SCT, suggesting that this should be further investigated. **However, research for use in children is in the early stages of development** [11]. While the mechanisms of action of stem cells are being elucidated by basic research and *in vivo* models, clinical trials are needed to provide scientific effectiveness for human applications.

Currently, several clinical trials have been performed to study stem cells' safety and efficacy in managing ASD [5]. These trials have used different types of stem cells and demonstrated the relative safety of use in individuals with autism. Some trials have suggested, using standardized metrics- i.e., Vineland Adaptive Behavior Scales, as well as caregiver reports, that there is improvement in behaviour and social interactions. However, the data is limited and lacks consistent and reproducible findings [12]. In a phase 1 open-label trial in 25 children with autism, a single intravenous infusion of umbilical cord blood cells obtained from the same individual was found to be safe. It was associated with improved social communication and behaviour, although the follow-up duration was short, around one year [13]. However, in another randomized, blinded, placebo-controlled crossover trial in 29 children with autism, although there were trends toward improvement, particularly in socialization, no statistically significant differences were found for any endpoints. There was minimal evidence of clinical effectiveness. As with the previous study, a long-term follow-up assessment was lacking [14]. There are several similar studies with limitations in the methodology and inconclusive results, which are overall suggestive of relative safety and the need for more data to conclude efficacy [3, 15].

In CP, there is also emerging evidence from small clinical trials. Several review articles have detailed the small collection of studies performed to date, with the vast majority being single arm and very small sample sizes [11, 16, 17, 18, 19]. Four systematic reviews were done in 2016, 2019, and 2020, using differing inclusion criteria. Each evaluated between 4-5 randomized clinical trials, with the total number of participants ranging from 189- 328, with fairly wide age ranges, varying severity, and types of CP included, with clear weaknesses and biases noted in the reviews [7, 11, 18, 19]. These meta-analyses and an additional review by *Vankeshwaram et al. 2020*, which reviewed any study of SCT in CP, all suggest that while there is a suggestion of short-term improvement in gross motor function, measured by standardized metrics, the sustainability and clear impact of SCT versus potential placebo effect remains unknown [7, 11, 18, 19]. It is worth noting, as well, that researchers are predominantly assessing spastic CP, with initial variable severity and wide age ranges, thus further limiting data interpretation [16]. Studies often include a component of physical therapy, which also confounds results [11]. Improvement in other domains is even more limited, with studies looking at cognitive changes in inconsistent and varied metrics, so there needs to be clear data to date [11]. A further limitation of comparing the previous research is that the type of cellular therapy and dosing varies across studies. Umbilical cord stem cell therapy has shown the most promise to date, but current data is only suggestive of its promising safety profile, without definite efficacy yet demonstrated [11].

Generally, research is in the early stages of using SCT in ASD and CP. Some promising findings are emerging, including the safety profile. However, this data is limited in quantity and notably derived from carefully selected patient populations for these clinical trials, without any understanding to date of how

SCT may be tolerated in children who do not meet the clinical trial criterion. It should be carefully considered as SCT is recognized to have the potential risk of neurologic deficits [17].

Limitations

Several limitations must be considered before the results of cellular therapy in ASD or CP can be accepted, generalized, and recommended for use. Most of these studies have included relatively small numbers of subjects and have used different types of stem cells from different sources, in different dosages, with different routes of administration of stem cells, and have utilized different scales and scores for measuring impact, with different durations of follow up. A meta-analysis of 113 different clinical trials in various neurodegenerative disorders concluded that randomized, double-blind, placebo-controlled studies remain essential to assess the efficacy of interventions [20, 21]. An editorial on this meta-analysis highlights the important limitations of the existing data, including the adverse events suffered in many of the treatment arms and the risk of bias towards less weighting of recruitment to the placebo arm [22].

Ethics

Stem cell therapy must be performed under strict laboratory and clinical guidelines and regulations. The International Association of Neurorestoratology has recently published the Clinical Cell Therapy Guidelines for Neurorestoration [21], which recommends details of standards of operation for personnel, facilities, and institutions that perform cell-based therapies, as well as the ethical requirements, documentation of procedure, and therapy; cell quality control, safety and efficacy evaluations; policy of repeated treatments; patient information, not charging patients for unproven therapies; basic principles of cell therapy; and publishing responsibility. These regulations are essential before the results of a trial can be accepted.

Furthermore, given the lack of sufficient evidence for SCT use in CP and ASD, the cellular therapies offered at private clinics around the globe are not part of clinically ethical practice. Such use of SCT, described as 'stem cell tourism', may not only lead to more adverse effects without clear benefits but also at a considerable financial cost to the family. Such clinics could be considered as taking advantage of caregivers and parents who are facing devastating conditions with their children and are desperate for hope [17, 22, 23, 24]. Surveys of parents of children with ASD and CP indicate that the hope SCT offers often outweighs the therapy's potential risks in the caregiver's mind [25], thus making them vulnerable to misrepresented data.

Conclusion

Currently, evidence for stem cell treatments in ASD and CP is limited. Early evidence is mixed, and further research in this field is warranted, with the need for more extensive trials with meticulous study design and methodology. These are necessary first to establish the safety and long-term efficacy of such treatments in children with ASD or CP, but also- should it become a viable therapy, to determine the appropriate type of cells, dosing, and route of administration to use. Research regarding these aspects of SCT remains very early and is, thus, still being prepared for broader clinical use. Any clinical practice offering such treatment outside regulated clinical trials is unethical.

ICNA Position Statement

Based on the currently available evidence, the ICNA recognizes that stem cell therapies for ASD and CP are under clinical trial investigations and may have a potential role in treating these conditions in the future. However, current evidence for stem cell treatment is limited and insufficient to recommend this therapy in a clinical setting; moreover, standardized administration routes and dosing have yet to be determined. There is a significant risk in private centres offering this treatment without further data and in touting benefits that are unproven. Carefully designed clinical trials of stem cell therapies with rigorous regulatory controls and ethics overview and with no cost to patients are required.

The ICNA does not endorse stem cell therapy for ASD or CP outside strictly regulated clinical research trials.

Competing interests

None.

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