

Commentary and Clinical Implications of “State of the Evidence Traffic Lights 2019: Systematic Review of Interventions for Preventing and Treating Children with Cerebral Palsy”

Iona Novak^{1,2*}, Madison CB Paton², Megan Finch-Edmondson², Nadia Badawi^{2,3}, Michael Fahey^{4,5}, Annate Velde², Ashleigh Hines², Leigha Dark⁶, Amanda Khamis², Maria Mc Namara², Emma Stanton², Cathy Morgan²

¹Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

²Cerebral Palsy Alliance Research Institute, Specialty of Child and Adolescent Health, Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

³Grace Centre for Newborn Care, Children’s Hospital at Westmead, Westmead, New South Wales, Australia

⁴Department of Paediatric Neurology, Monash Health, Melbourne, Australia

⁵Department of Paediatrics, Monash University, Melbourne, Australia

⁶Cerebral Palsy Alliance, Sydney, Australia

*Correspondence should be addressed to Iona Novak; iona.novak@sydney.edu.au

Received date: July 07, 2021, **Accepted date:** July 29, 2021

Copyright: © 2021 Novak I, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Keywords: Cerebral palsy; Evidence based; GRADE; Traffic light system

Introduction

Cerebral palsy is an umbrella term for a range of conditions affecting movement and posture and is the most common physical disability of childhood. There have been substantial advances in understanding the various etiological pathways of cerebral palsy, with increasing recognition of the role of genetics, *in vitro* fertilization and cytomegalovirus [1-3]. In contrast, preventable causes such as hypoxia and infection burden remain high in low to middle income countries, resulting in a higher prevalence of severe physical disability [4]. The incidence of cerebral palsy is declining, and severity is lessening in high income countries (1.4 per 1000 in Australia) [5]. In these countries, early diagnosis at 3-6 months of age followed by early intervention is becoming the new standard of care [6]. However, the estimated prevalence is almost three times greater in low to middle income countries (3.4 per 1000 in Bangladesh), with a late diagnosis at 5 years 2 months limiting opportunities for intervention [4].

In 2013, and again in 2019, we set out to systematically

summarize the whole of the cerebral palsy intervention evidence into a single paper [7,8]. The aim of these publications was to provide a helicopter view of the evidence base and to allow graded comparisons between interventions that aimed to achieve the same therapeutic outcome. To achieve this, we used the Cochrane, GRADE and Evidence Alert Traffic Light System methodologies [7,9,10].

The field has seen an exponential growth in the volume of evidence, with the efficacy evidence base almost tripling in a six-year period. In our 2013 systematic review we identified and included 166 articles, evaluating 64 discrete interventions, seeking to deliver 131 different treatment outcomes [7]. In 2019, we found an additional 247 articles, evaluating 182 interventions, seeking to deliver 393 outcomes [8]. Effective “green light” interventions for: (a) prevention include antenatal corticosteroids, magnesium sulphate, caffeine, and neonatal hypothermia; (b) rehabilitation include action observations, bimanual training, casting, constraint induced movement therapy, environmental enrichment, fitness training, goal directed training, hippotherapy, home programs, literacy interventions, mobility training, oral sensorimotor (+/- electrical stimulation), pressure care, strength training,

task-specific training, treadmill training (+/- partial body weight support) and weightbearing; (c) parent support include acceptance and commitment therapy and stepping stones triple P; and (d) medical and surgical management include anti-convulsants, bisphosphonates, botulinum toxin (+/- occupational therapy or casting), diazepam, dentistry, hip surveillance, intrathecal baclofen, scoliosis correction, selective dorsal rhizotomy, and umbilical cord blood cell therapy. There is no reason to think this growth in new knowledge about cerebral palsy treatments will slow down, meaning there are increasing intervention options for parents and clinicians to be aware of, and consider, during decision-making.

This paper will provide research updates since our 2020 systematic review on five foci including 1) genetic causal pathways and implication for practice, 2) early intervention to harness neuroplasticity, 3) motor interventions to improve function, 4) reading to advance cognition and communication, and 5) stem cell and regenerative medicine interventions. Where relevant, we also provide commentary on the clinical implications of the emerging research evidence.

Genetic Casual Pathways and Implication for Practice

In the past, the contribution of genetic abnormalities to cerebral palsy was considered minimal, accounting for only 1% of causal pathways and restricted to a few inherited conditions such as hereditary spastic paraplegia and some chromosomal or metabolic conditions. Population-based studies of newborn encephalopathy and cerebral palsy have highlighted that over a quarter of people with these conditions have co-existing major congenital disabilities, hinting at a substantial etiological role for genetic abnormalities [11,12]. Increasingly, neonatal intensive care specialists are requesting genetic investigation on babies with neonatal encephalopathy. A prospective study using whole-exome sequencing has confirmed genetic diagnosis among term babies with neonatal encephalopathy, including epileptic encephalopathy associated with autosomal dominant de novo variants in *SCN2A* (p.Met1545Val), *KCNQ2* (p.Asp212Tyr), and *GNAO1* (p.Gly40Arg), lipoic acid synthetase deficiency due to compound heterozygous variants in *LIAS* (p.Ala253Pro and p.His236Gln), and encephalopathy associated with an X-linked variant in *CUL4B* (p.Asn211Ser) [13]. Defining the genomic contributions will help us understand the etiologic pathways and potentially allow us to develop personalized neuroprotective treatment strategies in the future [13].

In recent years, the identification of genetic causal pathways to cerebral palsy has burgeoned, with important expanded specialties for geneticists and neurologists [1]. It

is now understood that the 40% of cases of cerebral palsy without a readily identifiable etiology [1,14] may have a heritable cause [1,15]. Genomic copy number variations (CNVs) are present in 10-31% of cerebral palsy cases [16-20]. Whole-exome sequencing studies have yielded known deleterious genetic variants in ~14% of cerebral palsy cases [21], with large cohort studies identifying 298 candidate genes for cerebral palsy from both known disease-associated genes and sporadic causes [15]. This study revealed a genetic overlap between cerebral palsy, autism spectrum disorder, intellectual disability and epilepsy, shedding light on the prevalence of these common comorbidities [15]. Identifying a genetic component to cerebral palsy may inform genetic counselling and family planning. Examples of personalized medicine resulting from genetic findings include ethosuximide for *GNB1* encephalopathy [22] and levodopa for *CTNNA1*/ β -catenin deficient dystonia [23]. In the future, genomics may better elucidate responders and non-responders to conventional treatments. For instance, there has already been a preliminary suggestion that genetic variation in dopamine level affects responsiveness to motor interventions [24].

Despite the increasing recognition of genomic contribution to cerebral palsy, testing is far from routine. Debate remains about which patients to test and whether panels or whole exome or genome are appropriate. Cohort studies have identified recurrent changes in genes associated with cellular migration and differentiation including *CTNNA1*, *KIF1A*, *GNAO1*, and *TUBA1A* [25]. Overlap between neurodevelopmental conditions is evident. Identifying a genomic contribution aids understanding of the cerebral palsy diagnosis. However, like epilepsy and autism, cerebral palsy is a clinical diagnosis for a group of non-degenerative conditions caused by changes to the developing brain. While there has been discussion in the literature about whether a genetic diagnosis supersedes a diagnosis of cerebral palsy, the majority view of those working in the field is that a clinical diagnosis should remain.

Early Intervention to Harness Neuroplasticity

With an accurate early diagnosis of cerebral palsy now possible in many cases, the evidence base for early intervention is rapidly expanding [6]. It is now feasible to conduct randomized trials in the first few months of life in infants with or at high risk of cerebral palsy. In the past, most of the early intervention evidence base was inexact because interventions were conducted in infants that may be at risk of disability (such as pre-term infants), however many would go on to have a typical outcome. This resulted in underpowered studies with no firm recommendations for infants with cerebral palsy. There is now an international clinical practice guideline for early intervention in infants 0-2 years with or at high risk of cerebral palsy [26]. This

clinical practice guideline makes 28 evidence-based recommendations across nine domains of development. Guideline recommendations were developed using the GRADE framework [9] based on 16 systematic reviews and 27 randomized controlled trials. Recommendations focus on: (i) skills development; (ii) complication prevention; and (iii) parent support [26].

Major findings of this guideline support three general principles for early intervention: i) immediate referral for intervention after a high risk of cerebral palsy diagnosis; ii) collaborative goal setting with parents, focusing on goals that are both task and context specific; and iii) prioritization of parent capacity building in order to support attachment [26]. “Green light” evidence is strongest for task-specific motor training interventions based on neuroplasticity principles, aligning with data reported in older children with cerebral palsy. In contrast, interventions based on passive handling techniques received a strong recommendation against (“red light”), consistent with data trends in older children. The early intervention guideline also gave a strong recommendation for cognitive interventions that are targeted, child active and provide a background of social interaction and enrichment. Of concern, there is still limited published data for interventions that target infant communication and feeding skills, and this is an area requiring urgent attention. Only conditional recommendations, often based on interpolated evidence from broader “high risk” groups, could be made for interventions to treat or to prevent common commodities and symptoms such as vision impairment, sleep disorders, abnormal muscle tone, and musculoskeletal impairments. Given the important influence that these impairments have on function and quality of life of individuals with cerebral palsy, it is critical for collaborative research to focus on closing these gaps.

The emergent data regarding sensitive periods for functional synaptic connectivity lends weight to the idea of commencing neurorehabilitation interventions as close to the timing of injury as possible [27]. In the coming years we expect to see new data from large clinical trials nearing completion and a rise in the number of clinical trials involving very early intervention, commencing in the NICU or in the first weeks of life [28,29].

Motor Interventions to Improve Function

A suite of interventions now exists that can improve motor function in children with cerebral palsy. “Green light” recommendations for children with cerebral palsy include mobility training, treadmill training, constraint induced movement therapy (CIMT), bimanual therapy, goal directed training, task specific training, action observation training and botulinum injections with occupational therapy [8]. Many of these evidence-based interventions apply the motor learning theory with experience-dependent

plasticity as the mechanism of action. The motor learning theory can be complex to understand and even more challenging to put into practice; therapy should be specific, with sufficient repetitions, intensity, and commenced as early as possible to train children to use and improve their own skills [30]. Task-specific interventions that actively involve the child either through functional, part-task or whole task goal-directed training are recommended.

For children with unilateral cerebral palsy, constraint induced movement therapy (CIMT) and bimanual therapy are examples of well-known and effective task-specific interventions, with recent evidence supporting treatment efficacy regardless of corticospinal tract connectivity [31]. Newer task-specific motor interventions include Hand Arm Bimanual Intensive Therapy – Including the Lower Extremity (HABIT-ILE) for children with bilateral cerebral palsy [32], and action-observation training for children with both unilateral and bilateral cerebral palsy. HABIT-ILE is a 90-hour training intervention offered in a day camp model. Action-observation training shows promise for augmenting upper limb function training effects by having the infant or child mimic demonstrations of successful actions on an object via activation of the mirror neuron system [33]. However, insufficient evidence is available to support using action-observations in isolation or above other task-specific interventions [34].

Intervention dose, or intensity is the amount of time required for a specific therapy. The result is also influenced by how long and how regularly the child actively practices a task, the level of challenge and variety but is also influenced by a range of individual, personal and environmental factors, such as motivation and enjoyment. Precisely ‘*how much*’ task-specific training is required to achieve best outcomes’ is an important question for children with cerebral palsy, their families, clinicians, and funding bodies. For children with cerebral palsy, Goal Directed Training (which might adjust child, task or environmental factors to improve goal performance) or Cognitive Orientation to Occupational Performance (which uses a problem-solving process to achieve child-set goals) that incorporates active practice of child-set goals requires 14 hours of therapy to achieve meaningful improvements [35]. Non-functional interventions, for example virtual reality gaming that practices a suite of movements, which is not focused on the practice of a specific child-set goal, requiring 40 hours of therapy; an extra 26 hours of therapy to achieve the same outcome. In this case, more therapy does not constitute greater improvements. Judiciously chosen motor interventions for children with cerebral palsy can protect a child and family’s time, funding, efforts and motivation levels. All of which are particularly important as levels of persistence and endurance are often compromised in children with cerebral palsy [36]. Directing funding into known effective interventions such as Goal Directed Training and/or Task-Specific training, is cost-effective,

and includes the potential to harness motivation through meaningful improvement in goals, and more free time for children and their families.

Reading to Advance Cognition and Communication

Children with cerebral palsy are at risk of comorbid intellectual disability, although prevalence is declining in high-income countries [37]. Additionally, speech and language difficulties are common, with motor and cognitive causes. There is strong evidence from meta-analyses that interactive reading raises IQ by 6-points in children aged under 4 years [38], and moderately improves expressive and receptive language (Cohen effect size 0.40-0.59 and 0.29, respectively) in typically developing children [39,40]. Consequently, interactive reading is recommended for all children from an early age as a cognitive and language intervention strategy [38,39].

Notwithstanding, very limited early reading research has been conducted in cerebral palsy. This may be due to a strong emphasis on walking in children’s early years, and is consistent with a paucity of research focusing on early development of communication in its many forms. One pilot randomized trial in infants with cerebral palsy including interactive reading within an environmental enrichment program, found higher cognitive skills at one-year of age in the ‘reading’ group [41]. Peeters et al., found speech intelligibility scores and fine motor skills of children with cerebral palsy to be predictive of a lower level of engagement in emergent literacy activity with their parents, less active participation in word-related activities during reading, and less interest in writing activities [42]. Parents of children with cerebral palsy were also unsure what to expect of their child’s literacy potential and needed support in implementing strategies to promote literacy development skills. As baseline cognition, language and speech impairment in cerebral palsy do not categorically preclude development of literacy skills, presuming competence by facilitating access to phonological and phonemic awareness instruction, accessible literacy software, and word-focussed interactive reading strategies appears critical.

For children with cerebral palsy with little or no functional speech, access to opportunities to practice, develop, and utilise literacy skills are severely limited or even impossible without assistive technology e.g. augmentative and alternative communication (AAC). Three recent systematic reviews [43-45] investigated the effects of instruction on single-word reading of individuals using AAC. Findings indicate that instruction using phonological awareness, sight word approaches, adapted book reading, and aided language stimulation were effective at improving single-word reading or spelling ability for children using AAC,

including children with cerebral palsy with or without intellectual disability. As such, AAC-mediated formal and informal literacy opportunities are a “green light” intervention and are essential to making literacy an accessible skill for this population.

AAC is considered a yellow light intervention with a small body of very low-quality evidence supporting its use in children with cerebral palsy to improve their communication, supplement verbal speech and increase peer interactions. However, a more robust evidence exists outside the cerebral palsy population [46], supporting targeting outcomes including (i) development of functional communication skills [47], (ii) improved expressive and receptive language and social skills [48], (iii) verbal speech development [49-51], and (iv) quality of life and independence [52].

With research showing that children with communication challenges do best when introduced to AAC as early as 12 months [53,54], a focus on the interconnection between enriched home literacy environments, early modelling and use of AAC within interactive reading activities, and influence on literacy outcomes, warrants further exploration.

Stem Cell and Regenerative Medicine Interventions

Stem cells and regenerative medicine are regarded as new interventions; prior to 2012, there was limited published clinical trial data available and as such, cell therapies did not appear in the original systematic review of interventions for cerebral palsy [7]. Now, stem cells have been used in research to treat cerebral palsy for more than 15 years [55]. Particularly in the last five years, we have seen publication of several randomized controlled trials investigating various cell therapies for cerebral palsy. To date, most clinical research has been conducted using umbilical cord blood (UCB) and we recently reported on the nearly 800 people with cerebral palsy treated with UCB in clinical studies [55].

The main mechanism of action of UCB for cerebral palsy is via immunomodulation and paracrine signaling [56]. This may prove particularly useful in at least a subset of children with cerebral palsy, who are known to have an altered and persistent inflammatory response [57]. UCB, coupled with rehabilitation, received a “green light” recommendation with moderate-quality evidence to indicate that this treatment is safe and can provide small but meaningful improvements in motor function in children with cerebral palsy [8]. However, UCB remains unapproved for the treatment of cerebral palsy. To enable regulatory approval and access, a Phase 3 trial of UCB is the next necessary research direction, with global leaders

in stem cell research for cerebral palsy supporting this call [58]. Future research is also required to optimize stem cell treatments and elucidate ideal cell dosage, number of doses, timing of treatment and to identify potential best-responders.

Stem cell therapies continue to be a significant area of interest for people with cerebral palsy and their families. Demand for access to these treatments is growing [59,60]. Accompanying registered clinical trials, Expanded Access Programs in the USA and Europe have enabled access to stem cell treatments for children with cerebral palsy since 2017 and 2019, respectively. Using this mechanism, more than 500 children with cerebral palsy have received cell therapies [61,62], although this is difficult to verify, and likely a significant underestimation, with numbers possibly in the thousands. In addition to patients accessing treatment via Expanded Access Programs and clinical trials, there has been a boom in direct-to-consumer marketing of unproven stem cell treatments via private clinics [63]. These clinics often function without regulatory oversight and patient safety is a genuine concern. People with cerebral palsy or their families also pay significant costs for these treatments which may include travel and other medical expenses, typically requiring upwards of US\$30,000 [60]. Even with known risks, patient demand for access to these private clinics continues to rise [64].

We know that clinicians are often asked about access to stem cell therapies for cerebral palsy, including via private clinics [65]. Clinicians therefore play an important role in supporting those with cerebral palsy and their families regarding stem cell and regenerative medicine options. We anticipate that once a Phase 3 trial is complete, UCB will become the first approved cell-based therapy for the treatment of cerebral palsy in the world. Until then, those with cerebral palsy and their families will seek advice to evaluate available information about stem cells and the research evidence. This may also include making decisions around accessing experimental stem cell treatments either via clinical trials or private clinics.

Conclusion

In conclusion, the evidence base for cerebral palsy is rapidly expanding. Prevention is now partially possible leading to a reduction in the incidence of cerebral palsy. Genetics is emerging as an important etiological factor and will most likely lead to the definition of cerebral palsy needing revision, as well as the emergence of new management options. Use of training-based interventions that focus on the child’s goals and involve high intensity repetition, with variety to induce neuroplasticity, are now the standard of care for improving function in children with cerebral palsy. Literacy interventions advance cognitive abilities that can improve wide-ranging outcomes and have been

under-utilized until now. Knowledge is growing about how to apply such interventions in infants following an early diagnosis and can improve children’s long-term outcomes, even altering the natural history of the condition. Hope is mounting from new regenerative medicine interventions such as stem cells that are immunomodulatory and stimulate neural repair to improve function.

Conflicts of Interest

All authors have no conflicts of interest to declare.

References

1. Fahey MC, MacLennan AH, Kretzschmar D, Geetz J, Kruer MC. The genetic basis of cerebral palsy. *Dev Med Child Neurol.* 2017;59(5):462-9.
2. Goldsmith S, McIntyre S, Badawi N, Hansen M. Cerebral palsy after assisted reproductive technology: a cohort study. *Dev Med Child Neurol.* 2018;60(1):73-80.
3. Smithers-Sheedy H, Raynes-Greenow C, Badawi N, Fernandez MA, Kesson A, McIntyre S, et al. Congenital Cytomegalovirus among Children with Cerebral Palsy. *J Pediatr.* 2017;181:267-71.e1.
4. Khandaker G, Muhit M, Karim T, Smithers-Sheedy H, Novak I, Jones C, et al. Epidemiology of cerebral palsy in Bangladesh: a population-based surveillance study. *Dev Med Child Neurol.* 2019;61(5):601-9.
5. Galea C, McIntyre S, Smithers-Sheedy H, Reid SM, Gibson C, Delacy M, et al. Cerebral palsy trends in Australia (1995–2009): a population-based observational study. *Dev Med Child Neurol.* 2019;61(2):186-93.
6. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. *JAMA Pediatr.* 2017;171(9):897-907.
7. Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol.* 2013;55(10):885-910.
8. Novak I, Morgan C, Fahey M, Finch-Edmondson M, Galea C, Hines A, et al. State of the Evidence Traffic Lights 2019: Systematic Review of Interventions for Preventing and Treating Children with Cerebral Palsy. *Curr Neurol Neurosci Rep.* 2020;20(2):3.
9. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and

transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ.* 2016;353:i2016.

10. Cochrane. Cochrane Handbook for Systematic Reviews of Interventions 2021. Available from: www.training.cochrane.org/handbook.

11. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *Bmj.* 1998;317(7172):1549-53.

12. McIntyre S, Blair E, Goldsmith S, Badawi N, Gibson C, Scott H, et al. Congenital anomalies in cerebral palsy: where to from here? *Dev Med Child Neurol.* 2016;58 Suppl 2:71-5.

13. Bruun TUJ, DesRoches CL, Wilson D, Chau V, Nakagawa T, Yamasaki M, et al. Prospective cohort study for identification of underlying genetic causes in neonatal encephalopathy using whole-exome sequencing. *Genet Med.* 2018;20(5):486-94.

14. Numata Y, Onuma A, Kobayashi Y, Sato-Shirai I, Tanaka S, Kobayashi S, et al. Brain magnetic resonance imaging and motor and intellectual functioning in 86 patients born at term with spastic diplegia. *Dev Med Child Neurol.* 2013;55(2):167-72.

15. Jin SC, Lewis SA, Bakhtiari S, Zeng X, Sierant MC, Shetty S, et al. Mutations disrupting neuritogenesis genes confer risk for cerebral palsy. *Nature Genetics.* 2020;52(10):1046-56.

16. Corbett MA, van Eyk CL, Webber DL, Bent SJ, Newman M, Harper K, et al. Pathogenic copy number variants that affect gene expression contribute to genomic burden in cerebral palsy. *npj Genet Med.* 2018;3(1):33.

17. McMichael G, Girirajan S, Moreno-De-Luca A, Gecz J, Shard C, Nguyen LS, et al. Rare copy number variation in cerebral palsy. *Eur J Hum Genet.* 2014;22(1):40-5.

18. Oskoui M, Gazzellone MJ, Thiruvahindrapuram B, Zarrei M, Andersen J, Wei J, et al. Clinically relevant copy number variations detected in cerebral palsy. *Nat Commun.* 2015;6:7949.

19. Segel R, Ben-Pazi H, Zeligson S, Fatal-Valevski A, Aran A, Gross-Tsur V, et al. Copy number variations in cryptogenic cerebral palsy. *Neurology.* 2015;84(16):1660-8.

20. Zarrei M, Fehlings DL, Mawjee K, Switzer L, Thiruvahindrapuram B, Walker S, et al. De novo and rare inherited copy-number variations in the hemiplegic form of cerebral palsy. *Genet Med.* 2018;20(2):172-80.

21. McMichael G, Bainbridge MN, Haan E, Corbett M, Gardner A, Thompson S, et al. Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy. *Mol Psychiatry.* 2015;20(2):176-82.

22. Colombo S, Petri S, Shalomov B, Reddy HP, Tabak G, Dhindsa RS, et al. G protein-coupled potassium channels implicated in mouse and cellular models of GNB1 Encephalopathy. *BioRxiv.* 2019:697235.

23. Pipo-Deveza J, Fehlings D, Chitayat D, Yoon G, Sroka H, Tein I. Rationale for dopa-responsive CTNNB1/ β -catenin deficient dystonia. *Mov Disord.* 2018;33(4):656-7.

24. Diaz Heijtz R, Almeida R, Eliasson AC, Forssberg H. Genetic Variation in the Dopamine System Influences Intervention Outcome in Children with Cerebral Palsy. *EBioMedicine.* 2018;28:162-7.

25. Moreno-De-Luca A, Millan F, Pesacreta DR, Elloumi HZ, Oetjens MT, Teigen C, et al. Molecular Diagnostic Yield of Exome Sequencing in Patients With Cerebral Palsy. *Jama.* 2021;325(5):467-75.

26. Morgan C, Fetters L, Adde L, Badawi N, Bancale A, Boyd RN, et al. Early Intervention for Children Aged 0 to 2 Years With or at High Risk of Cerebral Palsy: International Clinical Practice Guideline Based on Systematic Reviews. *JAMA Pediatrics.* 2021 May 17.

27. Ritterband-Rosenbaum A, Herskind A, Li X, Willerslev-Olsen M, Olsen MD, Farmer SF, et al. A critical period of corticomuscular and EMG-EMG coherence detection in healthy infants aged 9-25 weeks. *J Physiol.* 2017;595(8):2699-713.

28. Basu AP, Pearse J, Watson R, Dulson P, Baggaley J, Wright B, et al. Feasibility trial of an early therapy in perinatal stroke (eTIPS). *BMC Neurology.* 2018;18(1):102.

29. Dusing SC, Burnsed JC, Brown SE, Harper AD, Hendricks-Munoz KD, Stevenson RD, et al. Efficacy of Supporting Play Exploration and Early Development Intervention in the First Months of Life for Infants Born Very Preterm: 3-Arm Randomized Clinical Trial Protocol. *Phys Ther.* 2020;100(8):1343-52.

30. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res.* 2008;51(1):S225-39.

31. Friel KM, Ferre CL, Brandao M, Kuo H-C, Chin K, Hung Y-C, et al. Improvements in Upper Extremity Function Following Intensive Training Are Independent of Corticospinal Tract Organization in Children With Unilateral Spastic Cerebral Palsy: A Clinical Randomized Trial. *Frontiers in Neurology.* 2021;12(633).

32. Sakzewski L, Bleyenheuft Y, Boyd RN, Novak I, Elliott C, Reedman S, et al. Protocol for a multisite randomised trial of Hand–Arm Bimanual Intensive Training Including Lower Extremity training for children with bilateral cerebral palsy: HABIT-ILE Australia. *BMJ Open.* 2019;9(9):e032194.
33. Alamer A, Melese H, Adugna B. Effectiveness of Action Observation Training on Upper Limb Motor Function in Children with Hemiplegic Cerebral Palsy: A Systematic Review of Randomized Controlled Trials. *Pediatric Health Med Ther.* 2020;11:335-46.
34. Abdelhaleem N, Taher S, Mahmoud M, Hendawy A, Hamed M, Mortada H, et al. Effect of action observation therapy on motor function in children with cerebral palsy: a systematic review of randomized controlled trials with meta-analysis. *Clin Rehabil.* 2021;35(1):51-63.
35. Jackman M, Lannin N, Galea C, Sakzewski L, Miller L, Novak I. What is the threshold dose of upper limb training for children with cerebral palsy to improve function? A systematic review. *Australian Occupational Therapy Journal.* 2020;67(3):269-80.
36. Majnemer A, Shevell M, Law M, Poulin C, Rosenbaum P. Level of motivation in mastering challenging tasks in children with cerebral palsy. *Dev Med Child Neurol.* 2010;52(12):1120-6.
37. Australian Cerebral Palsy Register (ACPR) Group. Report of the Australian Cerebral Palsy Register, Birth years 1995-2012, November 2018. 2018. Available from: https://www.cpreregister.com/pubs/pdf/ACPR-Report_Web_2018.pdf
38. Protzko J, Aronson J, Blair C. How to Make a Young Child Smarter: Evidence From the Database of Raising Intelligence. *Perspect Psychol Sci.* 2013;8(1):25-40.
39. Dunst CJ, Simkus A, Hamby DW. Relationship between age of onset and frequency of reading and infants' and toddlers' early language and literacy development. *Center for Early Literacy Learning Reviews.* 2012;5(3):1-10.
40. Mol SE, Bus AG, de Jong MT, Smeets DJH. Added Value of Dialogic Parent–Child Book Readings: A Meta-Analysis. *Early Education and Development.* 2008;19(1):7-26.
41. Morgan C, Novak I, Dale RC, Guzzetta A, Badawi N. Single blind randomised controlled trial of GAME (Goals - Activity - Motor Enrichment) in infants at high risk of cerebral palsy. *Res Dev Disabil.* 2016;55:256-67.
42. Peeters M, Verhoeven L, de Moor J, van Balkom H, van Leeuwe J. Home literacy predictors of early reading development in children with cerebral palsy. *Res Dev Disabil.* 2009;30(3):445-61.
43. Barker MR, Saunders KJ, Brady NC. Reading instruction for children who use AAC: considerations in the pursuit of generalizable results. *Augment Altern Commun.* 2012;28(3):160-70.
44. Mandak K, Light J, Boyle S. The effects of literacy interventions on single-word reading for individuals who use aided AAC: a systematic review. *Augment Altern Commun.* 2018;34(3):206-18.
45. Stauter DW, Myers SR, Classen A. Literacy instruction for young children with severe speech and physical impairments: A systematic review. *Journal of Occupational Therapy, Schools, & Early Intervention.* 2017;10:389 - 407.
46. Crowe B, Machalicek W, Wei Q, Drew C, Ganz J. Augmentative and Alternative Communication for Children with Intellectual and Developmental Disability: A Mega-Review of the Literature. *Journal of Developmental and Physical Disabilities.* 2021.
47. Drager K, Light J, McNaughton D. Effects of AAC interventions on communication and language for young children with complex communication needs. *J Pediatr Rehabil Med.* 2010;3(4):303-10.
48. Light J, McNaughton D. Communicative Competence for Individuals who require Augmentative and Alternative Communication: A New Definition for a New Era of Communication? *Augmentative and Alternative Communication.* 2014;30(1):1-18.
49. Millar DC, Light JC, Schlosser RW. The Impact of Augmentative and Alternative Communication Intervention on the Speech Production of Individuals With Developmental Disabilities: A Research Review. *Journal of Speech, Language, and Hearing Research.* 2006;49(2):248-64.
50. Schlosser R, W., Wendt O. Effects of Augmentative and Alternative Communication Intervention on Speech Production in Children With Autism: A Systematic Review. *American Journal of Speech-Language Pathology.* 2008;17(3):212-30.
51. Walters C, Sevcik RA, Ronski M. Spoken Vocabulary Outcomes of Toddlers With Developmental Delay After Parent-Implemented Augmented Language Intervention. *Am J Speech Lang Pathol.* 2021;30(3):1023-37.
52. World Health Organisation. World Report on Disability. Geneva; 2011. Available from: https://www.who.int/disabilities/world_report/2011/accessible_en.pdf
-

53. Branson D, Demchak M. The Use of Augmentative and Alternative Communication Methods with Infants and Toddlers with Disabilities: A Research Review. *Augmentative and Alternative Communication.* 2009;25(4):274-86.

54. Light J, Drager K. AAC technologies for young children with complex communication needs: State of the science and future research directions. *Augmentative and Alternative Communication.* 2007;23(3):204-16.

55. Paton MCB, Finch-Edmondson M, Fahey MC, London J, Badawi N, Novak I. Fifteen years of human research using stem cells for cerebral palsy: A review of the research landscape. *Journal of Paediatrics and Child Health.* 2021;57(2):295-6.

56. Sun JM, Kurtzberg J. Stem cell therapies in cerebral palsy and autism spectrum disorder. *Developmental Medicine & Child Neurology.* 2021;63(5):503-10.

57. Zareen Z, Strickland T, Fallah L, McEneaney V, Kelly L, McDonald D, et al. Cytokine dysregulation in children with cerebral palsy. *Developmental Medicine & Child Neurology.* 2021;63(4):407-12.

58. Sun J, Case L, McLaughlin CA, Burgess A, Skergan N, Cash J, et al. 215 - A Randomized Trial Comparing Umbilical Cord Blood and Cord Tissue Mesenchymal Stromal Cells in Young Children with Cerebral Palsy. *Transplantation and Cellular Therapy.* 2021;27(3, Supplement):S195.

59. Ruff CA, Faulkner SD, Fehlings MG. The potential for

stem cell therapies to have an impact on cerebral palsy: opportunities and limitations. *Dev Med Child Neurol.* 2013;55(8):689-97.

60. Snyder J, Turner L. Crowdfunding for stem cell-based interventions to treat neurologic diseases and injuries. *Neurology.* 2019;93(6):252.

61. FamiCord Suisse. List of life saving transplantations: FamiCord Group; 2019 [Available from: <https://famicord.lu/en/about-us/list-of-life-saving-transplantations>].

62. Frances Verter. Cerebral Palsy Expanded Access Program in Europe: Parent’s Guide to Cord Blood Foundation; 2019 [Available from: <https://parentsguidecordblood.org/en/news/cerebral-palsy-expanded-access-program-europe>].

63. Zarzeczny A, Atkins H, Illes J, Kimmelman J, Master Z, Robillard JM, et al. The stem cell market and policy options: a call for clarity. *Journal of Law and the Biosciences.* 2018;5(3):743-58.

64. Petersen A, Munsie M, Tanner C, MacGregor C, Brophy J. *Stem Cell Tourism and the Political Economy of Hope.* 1 ed: Palgrave Macmillan UK; 2017.

65. Paton MCB, Finch-Edmondson M, Galea C, Garrity N, Fahey MC, Novak I. Education can improve clinician confidence in information sharing and willingness to refer to stem cell clinical trials for cerebral palsy. *J Investig Med.* 2021.