ABSTRACT

Cerebral palsy is a static encephalopathy with multiple etiologies. Several interventions toward perinatal risk factors, intrapartum asphyxia, and head injury or infection have been evaluated in order to deal with irreversible brain damage. Antenatal–intrapartum and neonatal interventions mainly focus on preventing hypoxia, oxidative stress, inflammation, and growth restriction. Among these preventive interventions, magnesium sulfate for neuroprotection of the fetus in women at risk of preterm birth and therapeutic hypothermia (cooling of body or just brain) for newborns with hypoxic–ischemic encephalopathy have effectively reduced cerebral palsy risk. There is still a lack of literature on the effectiveness of preventive interventions toward postnatally acquired brain injury. Social pediatricians are concerned with identifying, reducing, or eliminating risk factors of cerebral palsy and encourage a comprehensive approach to providing integrated and personalized care to children with cerebral palsy with the support of their families and communities.

Keywords: Cerebral palsy, intervention, prevention

INTRODUCTION

Cerebral palsy (CP) is a static encephalopathy that occurs as a result of irreversible damage to the immature brain in the prenatal–perinatal–early postnatal period. Impaired control of movement and posture is the main clinical and pathophysiological feature. The brain injury leading to motor impairment occurred prenatally, at birth, or shortly after birth, and motor dysfunction is permanent. Abnormal muscle tone, posture, and movement limit the individuals’ activity and motor disability is often accompanied by comorbidities.1,2

CEREBRAL PALSY

Epidemiology

Although the prevalence of CP varies between populations, the estimated global prevalence is about 3.16% in children (birth prevalence = 1.5–4 per 1000 live births).2,3 Consistently, in Turkey, the prevalence of CP was found to be 4.4 per 1000 live births.4 The incidence of CP has been suggested to be decreasing in some developed nations through neuroprotective strategies in neonatal brain injury.5 Racial disparities were determined in the changes of the CP prevalence and the prevalence was reported to be decreased for a term, stable for preterm, and increased for very preterm/extremely low birth weight neonates.6,7 Sex has been reported to have an effect on the incidence of CP with a male/female ratio of 1.3 : 1 to 1.4 : 1, and no equalization has been detected in the incidence of CP between genders during recent years.8

Risk Factors

Cerebral palsy has multiple etiologies; while 92% of cases are attributable to perinatal risk factors and 8% to head injury or infection at an older age. Fewer than 10% of cases with...
Table 1. Common Risk Factors for Cerebral Palsy

| Prenatal                          | Perinatal                          | Postnatal                        |
|----------------------------------|------------------------------------|----------------------------------|
| Maternal factors: TORCH infection, maternal hypothyroidism, iodine deficiency, thrombotic disorders, chorioamnionitis, use of preterm antibiotics before rupture of membranes, early onset preeclampsia | Birth hypoxia and trauma           | Hyperbilirubinemia                |
| Fetal factors: teratogen exposure, genetic and metabolic disorders, multiple births, prematurity, intrauterine growth restriction, low birth weight, post-maturity, congenital malformations | Asphyxia and acidosis             | Neonatal sepsis                   |
| Social factors: low socioeconomic status | Non-vertex presentation            | Respiratory distress              |
|                                  | Placental abruption                | Early onset meningitis            |
|                                  | Rupture of the uterus              | Intraventricular hemorrhage       |
|                                  | Prolonged or obstructed labor      | Periventricular leukomalacia       |
|                                  | Arterial ischemic stroke           | Neonatal stroke                   |
|                                  |                                     | Head injuries 2-5 years before (a cerebrovascular accident, spontaneous, associated with surgery or with complications of cardiac defects, or accidental and non-accidental injuries) |

Genetic contributions: several candidate genes associated with process of inflammation, coagulation and blood flow, and normal fetal neurodevelopment; mutations in single genes and strong inheritance patterns, most often autosomal recessive, in certain specific CP forms.

perinatal risk factors are attributed to intrapartum hypoxia.\textsuperscript{1,2} Gestational hypertension, rupture of gestational membranes prior to the onset of labor, emergency cesarean section, and preterm birth have recently been identified as risk factors for CP in children.\textsuperscript{3} Table 1 presents common risk factors for CP. The mechanisms leading to CP should be understood to develop strategies for the reduction of CP and identify prevention modalities. Underlying mechanisms leading to CP are shown in Figure 1.

Clinical Management

The main clinical manifestations of CP are abnormal movement, posture, and balance. Also, sensory and perceptual deficits occur. Additional clinical findings include communication difficulties, gastrointestinal problems, hearing and vision abnormalities, impaired oral–motor function, behavioral and emotional issues, psychiatric comorbidities, cognitive impairment, speech impairment, osteoporosis, pressure ulcers, seizures, and urinary incontinence. The diagnosis of CP is clinical through history and physical examination. Magnetic resonance imaging may demonstrate intracranial abnormalities. After establishing the diagnosis, the severity of CP can be evaluated using various CP assessment tools. Treatment approaches are focused on spasticity and dystonia, hip pain and dislocation, balance problems, hand dysfunction, equines deformity, and nutritional inadequacy. Response to treatment can also be monitored by using CP assessment tools.\textsuperscript{4} The Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) questionnaire is an evaluation scale for severely affected children with CP, and the Turkish version of the CPCHILD has already been developed to evaluate the health-related quality of life of children with CP.\textsuperscript{9}

Antenatal and Intrapartum Prevention

In the antenatal period, placental insufficiency, infection, non-infectious inflammation, imbalanced and insufficient nutrition, and maternal physical or psychosocial stress lead to perinatal brain damage through mitochondrial dysfunction (apoptosis), excitotoxicity, and oxidative stress (neuroinflammation). The interventions target ameliorating cerebral vasculature and preserving brain cells (neurons, astrocytes, oligodendrocytes, and microglia) from apoptotic and necrotic cell death.\textsuperscript{10}

Figure 1. Mechanisms leading to cerebral palsy.
At this stage, for preventing CP, social pediatricians argue for comprehensive care for expectant pregnant, pregnant, or recently pregnant women including (i) vaccination for preventable diseases and screening and monitoring for treatable conditions, (ii) counseling about preventive health behaviors of good nutrition, physical activity, personal hygiene, avoided or eliminated the use of tobacco/consumption of alcohol, regular complete physical examination, and following directions for taking prescribed medications, (iii) counseling about safety and injury prevention, and sexual-reproductive health, and (iv) psychological and social support.

**Potential Treatments**

Whether intrauterine infection, placental, and fetal inflammation, gray and white matter damage, and preterm birth may be reduced by candidate therapeutic agents is an ongoing question for researchers who study the preventive strategies for CP. Potential treatment strategies for the antenatal and intrapartum prevention of CP are presented in Table 2.10 Social Pediatrician encourages multidisciplinary teams to discuss the effectiveness and accessibility of candidate therapeutic agents for preventing/minimizing permanent brain damage in the medical, ethical, economic, and social contexts.

**Perinatal Care**

In high-income countries, the birth prevalence of CP decreased by 35% in recent decades. Advances in perinatal care have contributed to this reduction. Reducing the rate of preterm birth and intrauterine growth restriction, preventing congenital anomalies and congenital infections, and improving neonatal intensive care unit and post-discharge follow-up services are the main perinatal care strategies that contributed to the decline in the birth prevalence of CP (Table 3). However, in the matter of CP, low awareness, insufficient practices for prevention, early detection and intervention, and lack of robust data, and statistics services are burning issues in low- and middle-income countries.10-12

From a social pediatrician perspective, national health policies should include perinatal care strategies involving preterm birth prevention modalities supported by primary healthcare practices for women. A perinatal care strategy involving genomic technologies, education and public health practices for pregnant females, neonatal screening for brain-damaging congenital infections, advanced neuroimaging, and neuroprotective modalities, and collaboration among families and healthcare providers within community support seem crucial for the prevention of CP.

**Antenatal and Intrapartum Interventions**

The antenatal and intrapartum preventive strategies for CP focus on dealing with infection and inflammation, hypoxia and oxidative stress, and preterm birth and fetal growth restriction. The effects of antenatal and intrapartum interventions for preventing CP are summarized in Table 4.12 Social Pediatrics campaigns for developing strategies to provide nation- and worldwide utilization of effective interventions reducing CP risk and to prevent utilization of interventions increasing CP risk in all medical settings.

**Neonatal Prevention**

The neonatal preventive strategies for CP focus on dealing with hypoxia and oxidative stress, acute and chronic conditions, infection and inflammation, and growth and developmental delay. The effects of neonatal interventions for preventing CP are summarized in Table 5.13

**Treating Asphyxia**

Therapeutic hypothermia in encephalopathic asphyxiated newborns provided a significant reduction in CP compared
Table 3. Perinatal Practices Increasing Awareness of Cerebral Palsy and Improving Perinatal Care for Preventing Brain Injury\(^{10-12}\)

| Preventing prenatal/perinatal brain injury | Preterm infant care | Term/near-term infant care | Pregnant care | Early intervention |
|-------------------------------------------|---------------------|----------------------------|---------------|-------------------|
|                                           | The implantation of 1 embryo by in vitro fertilization | Magnesium sulfate for neuroprotection | Corticosteroids for lung maturation | Improved resuscitation and less-invasive mechanical ventilation |
|                                           | Delayed cord clamping | Caffeine for apnea | Dealing with preterm labor: midwife-led continuity models of care for all women, zinc supplementation for pregnant women without systemic illness, antenatal lower genital tract infection screening for women without signs of preterm labor, cervical cerclage for women with singleton pregnancy and high risk of preterm birth | Identifying infants at high risk of CP in the first months of life and collaborating with these infants’ families in both neonatal intensive care unit and post-discharge visits |
|                                           | Improved resuscitation and less-invasive mechanical ventilation | Magnesium sulfate for neuroprotection | Corticosteroids for lung maturation | A perinatal care strategy involving genomic technologies, education, and public health practices about preventable congenital infections for pregnant females |
|                                           |迟延结扎 |咖啡因用于呼吸暂停 |用镁硫酸盐和皮质类固醇进行神经保护 |新生儿筛查致脑损伤的先天性感染 |

Table 4. Antenatal and Intrapartum Interventions for Preventing Cerebral Palsy\(^{12}\)

| Interventions for Dealing with | Evidence-Based Interventions |
|------------------------------|------------------------------|
| Infection and Inflammation   | One effective intervention reducing CP risk*: magnesium sulfate versus placebo for children born to women at risk of preterm birth |
| Hypoxia and Oxidative Stress | Two probably ineffective interventions increasing CP risk**: any preventive antibiotics versus no antibiotics for women in preterm labor when their waters have not broken; immediate birth versus deferred birth for preterm babies with suspected compromise |
| Preterm Birth and Fetal Growth Restriction | One probably ineffective intervention not making a clear difference in CP risk**: more than one course of corticosteroids versus a single course for women at risk of preterm birth |
| Antenatal and intrapartum interventions | No conclusions possible***: interventionist (early delivery) care versus expectant (delayed delivery) care for severe preeclampsia; magnesium sulfate versus placebo for women with preeclampsia; continuous cardiotocography versus intermittent auscultation for fetal assessment during labor; progesterone versus placebo for women with a previous history of spontaneous preterm birth; betamimetics versus placebo for inhibiting preterm labor; phenobarbital versus placebo for women at risk of very preterm birth |
| treating mild to moderate hypertension | No conclusions possible****: any antihypertensive drug or a beta-blocker versus placebo for women with mild to moderate hypertension during pregnancy; magnesium sulfate versus other tocolytic agents for preventing preterm birth in threatened preterm labor; vitamin K versus placebo for women at risk of imminent very preterm birth |

*High-quality evidence, **Moderate-quality evidence, ***Low-quality evidence, ****Very low-quality evidence.
should focus on reliably managing complications arising from sustained from infancy to childhood. Rehabilitation services should find out the reasons for reduced CP risk not being long-term follow-up of these children. Multidisciplinary teams treated newborns to therapeutic hypothermia and exhaustive should provide equal access to all encephalopathic asphyxiasthe burden of CP caused by intrapartum and postpartum brain damage, therapeutic hypothermia should be prioritized since undeveloped and developing countries have the high-est burden of CP at 6-7 years of age between therapeutic hypothermia and standard care groups. Therefore, since undeveloped and developing countries have the highest burden of CP caused by intrapartum and postpartum brain damage, therapeutic hypothermia should be prioritized in all regions of these countries. Medical and social policies should provide equal access to all encephalopathic asphyxiated newborns to therapeutic hypothermia and exhaustive long-term follow-up of these children. Multidisciplinary teams should find out the reasons for reduced CP risk not being sustained from infancy to childhood. Rehabilitation services should focus on reliably managing complications arising from perinatal encephalopathic asphyxia and sustaining the success of therapeutic hypothermia.

**Mechanical Ventilation**

The effects of prophylactic methylnanthine to stimulate breathing in preterm infants being weaned from mechanical ventilation have been assessed. Compared to placebo, a lower rate of CP at 18-21 months was determined in the caffeine group [RR (95% CI): 0.54 (0.32-0.92)]. A trial demonstrated that the risk of spastic CP at 2 years corrected age was found to be significantly lower for preterm infants ventilated with high-frequency oscillatory ventilation as compared to conventional ventilation (4% vs. 17%; [RR (95% CI): 0.87 (0.79-0.96)]. Then, gathering practice-based evidence should continue. In the meantime, health management authorities may perform a cost-effectiveness analysis of possibly effective interventions reducing CP risk.
Dealing with Hypoxia and Oxidative Stress

The effect of inhaled nitric oxide for pulmonary dysfunction in preterm newborns or newborns with a diaphragmatic hernia, caffeine for treatment or prevention of apnea in preterm infants, early volume expansion to provide cardiovascular support in very preterm infants, specific inotropes for hypotension in very preterm infants, and room air versus 100% oxygen for resuscitation on neurodevelopmental outcomes has been assessed. The risk for CP at 18–24 months did not significantly differ between the experimental and placebo/no treatment groups. Also, in the neonatal intensive care unit, reducing the sound levels that reach the individual neonate by using silicone earplugs (with the aim of preventing apnea, hypoxemia, and oxygen desaturation caused by nausea) did not affect the risk for CP at 18–22 months. Then, CP prevention strategies may force refraining from throwing financial, physical, and workforce sources at these probably ineffective or unfavorable interventions.

Dealing with Short-Term Conditions Linked to Premature Birth

With early (<8 days of age) corticosteroids for prevention of chronic lung disease, CP was found to be increased from 11 months to 7–9 years of age [RR (95% CI): 1.45 (1.06–1.98)], for dexamethasone RR 1.75 (1.2–2.55) and hydrocortisone RR 0.97 (0.55–1.69) but a nonsignificant increase was found in the combined outcome, death or CP. Besides, late (>7 days of age) administration of corticosteroids for the treatment of chronic lung disease did not affect the risk of CP or the combined outcome, death or CP at 1–3 years or the latest age reported (1 year up to 17 years). Also, no difference in CP risk in long-term follow-up was found between those preterm infants who received moderately early (7–14 days) postnatal corticosteroids for preventing chronic lung disease and those who received placebo or no treatment. Then, neonatal treatment practices should not increase the risk of CP just because corticosteroids reduce the risk of chronic lung disease. Cerebral palsy prevention strategies should include enhancing the knowledge of physicians about long-term neurological adverse effects of early postnatal therapies.

Since ethamsylate, a synthetic hemostatic drug promoting platelet adhesion and increasing the stability of the capillary basement membrane, decreases blood loss in certain clinical situations, whether it may reduce intracranial hemorrhage in preterm or very low birth weight infants has been assessed. No significant difference was found in the rates of CP at 2–4 years between those infants who received ethamsylate and those who did not. Also, postnatal administration of phenobarbital as a safe treatment that stabilizes cerebral blood flow and may protect against reperfusion damage did not reduce the risk of severe neurodevelopmental impairment including CP at 27 months. Likewise, no significant difference was found in the rates of CP at 18–54 months or at school age between those infants who received prophylactic indomethacin for patent ductus arteriosus (PDA) and those who did not.

Also, no significant difference was found in the rates of CP at 18–24 months between the infants who received oral and those who received intravenous ibuprofen for the treatment of PDA. The risk for CP at 1 year did not significantly differ between the preterm infants who were treated with synthetic surfactant and those who received a placebo. Also, prophylactic administration of protein-free synthetic surfactant in preterm newborns did not reduce the risk of CP at 12–24 months. The risk for major neural developmental impairment including CP at 1 year corrected age did not significantly differ between those preterm infants with or without respiratory distress syndrome (RDS) who received inositol for promoting maturation of the surfactant and those who did not. Also, the risk for CP at approximately 2 years corrected age did not significantly differ between those infants who received porcine surfactant extract and those who did not. No statistically significant difference in the rate of CP at 18 months was observed between the infants who received prophylactic phototherapy for the prevention of bilirubin encephalopathy and those who did not. Likewise, the risk for CP at 18–22 months corrected age did not significantly differ between the infants who received early (<8 days of age) darbepoetin alfa (a slightly modified long-acting version of erythropoietin) or erythropoietin for preventing anemia and those who received placebo or no treatment. Among very low birth weight infants, a restrictive blood transfusion strategy did not reduce the risk of CP at 18–21 months compared with a liberal blood transfusion strategy. The risk for CP at the post-menstrual age of 36 months did not significantly differ between the infants who received arginine supplementation for prevention of necrotizing enterocolitis (NEC) and those who received a placebo. Also, prophylactic enteral probiotics administration for prevention of severe NEC or sepsis, or both, in preterm infants did not affect the rate for mental retardation and CP at 18 months corrected age or later. Then, preventing CP does not seem possible with these interventions for preventing or treating short-term conditions linked to premature birth. In addition to routine treatment, early rehabilitation interventions like sensorial and motor stimulation, physiotherapy, and parent training for positioning and handling can be made widespread in the neonatal intensive care unit. Also, a national early rehabilitation home program can be designed with a CP preventative approach.

Dealing with Endocrine Disorders

Transient hypothyroxinemia in preterm infants in the first weeks of life has been shown to be linked to abnormal neurodevelopment. However, the risk for CP at 5.7 years did not significantly differ between the infants who received prophylactic T4 and those who received a placebo. Also, no difference was observed in CP risk at 2 years or older between the intervention group who received dextrose gel in the buccal mucosa and the control group who received placebo gel for rapidly correcting neonatal low blood glucose levels. Complex etiopathogenesis of CP makes establishing a single endocrine or metabolic cause and CP relationship difficult. Then, neonatal screening practice for endocrine and metabolic disorders should be strengthened and the screening program should be expanded. For global prevention of CP, not only developed countries but also least developed countries should have access to effective neonatal screening programs.

Dealing with Infection

The risk for CP at 18–22 months did not significantly differ between the infants who received prophylactic systemic antifungal agents for prevention of invasive fungal infection and those who received placebo or no drug. No difference was observed in CP risk at 3 years between the acyclovir and...
Dealing with Growth and Developmental Delay

Kangaroo mother care has been developed as an alternative to the conventional contemporary method of care for low birth weight infants. The components of kangaroo mother care are skin-to-skin contact, frequent and exclusive or nearly exclusive breastfeeding, and attempts at early discharge from the hospital, regardless of weight or gestational age, with strict follow-up. When the beneficial and adverse effects of kangaroo mother care were assessed, it was demonstrated that the risk for CP at 12 months corrected age did not significantly differ between the infants who received kangaroo mother care and those who received conventional neonatal care. Likewise, the rate of CP at 18 months to 6 years did not significantly differ between the infants who received the early developmental intervention and those who received standard medical follow-up. Also, the commencement of intervention (inpatient or post-hospital discharge) or focus of intervention (parent-infant relationship, parent-infant relationship and infant development, or infant development) did not affect the rate of CP. Even though no conclusions are possible for these interventions in preventing CP for now, a social pediatrician promotes early parent-baby bonding and early child development initiatives.

Postnatal Prevention

Vaccinations avoiding meningitides, improving perioperative care for congenital anomalies, implementing public health policies for child safety, and shaken baby prevention education may be potential interventions for reducing CP risk. However, there is a lack of literature on the effectiveness of interventions toward postnatally acquired brain injury. As a part of CP prevention strategies, social pediatrics recommend vaccines which prevent meningitides and encephalitis for all children and defend that the routine immunization schedules include these vaccines. Also, child protection and CP prevention systems should collaborate on the protection and promotion of the rights of children which protect them from neglect and abuse.

CONCLUSION

We have presented prospects for antenatal, natal, and neonatal interventions that could prevent CP. Both experimental and clinical approaches we have reviewed have been mainly evaluated for use in dealing with preterm birth and fetal/neonatal hypoxia and infection. Countries should prioritize preventive interventions by considering their development level and burden of CP and the common timing of brain damage causing CP in their nations. In all medical settings, a multidisciplinary team including medical genetics specialist, perinatologist, neonatologist, pediatric neurologist, social pediatrician, physical therapist, child development specialist, and social service specialist should collaborate to improve pregnant, neonate, and child care for preventing brain damage and for minimizing the burden of brain injury if it has already occurred.

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