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Dyskinetic cerebral palsy in children: Perspectives from low-resource settings

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Abstract

The information on dyskinetic cerebral palsy (DCP), including the fundamental epidemiological features, clinical presentations, radiological patterns of injury, the magnitude of motor disability, neurological outcomes, and the impact of chronic disability on the quality of life of the individual, family, and society, is derived from registries and studies from high-income countries. Despite a presumed higher burden of CP, there is a paucity of studies from low-resource settings, especially on DCP. The high-income countries have robust epidemiological and clinical data, facilitating early rehabilitation and reintegration into society, the predominance of genetic causes, and established preventive therapies. On the contrary, there is a greater burden of cases in low-resource settings, with limited rehabilitation options, late detection, the dominance of acquired and preventable causes, and limited management options in the chronic care of these patients. The dearth of resources is also reflected in the generation of research data using standardized scales of assessment and uniformity of definitions. The current brief review on the topic focuses on the perspectives from low-resource settings in the diagnosis and management of children with DCP. The paper is a summary of the presentation in the symposium on "Perspectives from Low Resource Settings" at the International Child Neurology Congress 2022, in Antalya, Turkey, in October 2022. The main objective of the symposium and subsequent studies is to help the readers identify challenges related to specific pediatric neurological disorders in resource-limited settings and to identify key areas of research in DCP.

Keywords: Cerebral palsy, dystonia, choreoathetosis, neurodevelopment, comorbidities.

Introduction

Dyskinetic cerebral palsy (DCP) is one of the most incapacitating forms of CP that is characterized by involuntary, recurrent, hyperkinetic movements and/or abnormal patterns of posture due to a static insult to the growing brain [1]. Up to 80% of the cases are of the dystonic subtype, and the rest are the choreoathetotic subtype.

DCP constitutes 6.5–15% of the total burden of CP [2, 3]. Surveillance of cerebral palsy in Europe describes an increasing prevalence of DCP (from 0.08 in the 1970s to 0.14 per 1000 live births in the 1990s) [4]. Its prevalence varies across different CP registries: 3% in Northern Ireland, 6% in Norway, 6.5% in Turkey and Quebec, and 16% in Sweden [4–6]. The crude incidences were 0.24 for DCP, 0.07 for choreo-athetoid CP, and 0.17 for dystonic CP per 1000 live births [7]. Due to the lack of standardized registries in low-resource regions, DCP has been noted to constitute 7–8% of the total CP cases in center-based studies [8, 9]. A higher prevalence of DCP (19–28%) has been seen in China [10]. The proportion of children with athetoid CP has been estimated to be 5.8% and those with rigidity were 1.7% [11]. The difference in prevalence may be due to the varying diagnostic routines and difficulties in differentiating between dominant spasticity and dystonia [4].

It is important to recognize DCP owing to its distinctive clinical and radiological features and the severity of motor dysfunction. Although less common than spastic CP, DCP is associated with severe motor disability that continues into adulthood, and dystonia has a significant impact on functional abilities [12]. They are predisposed to worsening dystonia and life-threatening status dystonicus [13]. It is often difficult to distinguish dyskinesia from spastic quadriparesis due to a nonuniform assessment or the coexistence of both types of motor dysfunction in the same patient. While the incidence and prevalence of DCP is relatively low when compared to "spastic" CP, most children with spastic CP have some degree of dystonia. Thus, mixed CP is often the correct phenotype than a pure spastic CP, and the presence of dystonia is likely to be a major contributor to disability even in children with prominent spasticity. This view was proposed as early as 1959 by Crothers and Paine based on their unique natural history study of 1800 individuals with CP examined between 1930 and 1950, and it continues to be true that there is not a high wall between spasticity and dystonia, but that most individuals with CP fall along a spectrum from "mostly spastic" to "mostly dyskinetic" [14]. The quantification of dystonia often needs standardized scales, which are often not routinely used. Although the interest in DCP is rising, there is a paucity of data from the low-resource settings on the clinical

course, radiological features, comorbidities, and outcomes in children with DCP [15, 16].

Etiology

Data from European registries indicate that DCP is predominantly seen in term-born, appropriate-for-gestational-age children who experienced adverse perinatal events [17–19]. The insult to the nervous system is perinatal in two-thirds and prenatal in one-fifth of the cases with DCP [17]. Hypoxic ischemic encephalopathy (HIE) has been the principal cause of DCP in developed countries. A study of 22 children with DCP showed that 16 had perinatal asphyxia, 4 had no association with predisposing conditions, and only 2 had neonatal jaundice [20]. A similar report on 115 children with DCP (11%) from 1056 total CP cases from a UK registry between 1967 and 1984 identified 17 term-born cases for the evaluation of etiological factors [21]. Ten (59%) of these children had evidence of fetal distress during labor, birth asphyxia, and HIE, two (12%) were severely jaundiced requiring several exchange transfusions, four were idiopathic, and one was a neurometabolic disorder. Similar other series of a small number of children with DCP shows a dearth of cases with hyperbilirubinemia as a cause [22, 23]. A recent study from Norway showed that perinatal risk factors such as term birth, low Apgar scores at 5 minutes, uterine rupture, umbilical cord complications, and potential sentinel events were more common among children with DCP compared to spastic diplegic CP [24].

Hyperbilirubinemia and ensuing DCP have almost disappeared in the developed regions, owing to the advancements in the management of neonatal hyperbilirubinemia and Rh-isoimmunized pregnancies [7, 18, 19]. It continues to appear at a low rate, partly due to the practice of early (<48 hours) discharge of newborns, resulting in readmissions for bilirubin encephalopathy [7, 17, 25]. The majority of cases are now secondary to birth asphyxia and/or neonatal seizures [4, 18, 20]. A risk of familial recurrence has been suggested by Amor et al. [26] who studied 22 patients with DCP, of which nearly 72% had a familial recurrence of athetoid CP with possible autosomal-recessive or X-linked-recessive inheritance. These cases were typically associated with significant spasticity, microcephaly, intellectual disability, seizures, and lack of birth asphyxia. The risk of recurrence in siblings may suggest a genetic contribution to dyskinesia [26].

In developing countries, hyperbilirubinemia-induced DCP contributes to nearly one-third of the acquired and preventable causes of CP [8, 9, 15]. In the resource-poor regions, the major contributors to DCP are neonatal hyperbilirubinemia (78.5%), asphyxia (2.6%), and combined insults (4.4%) [9, 15]. Neonatal seizures are less commonly reported (20%) as compared to the western figures of 75–83% [4, 18]. DCP may be multifactorial in a few cases, and the dominant insult may be difficult to ascertain [17]. In our previous study on children with DCP, the major causes of DCP were hyperbilirubinemia, followed by perinatal asphyxia overall as well as in the dystonic and choreoathetosis subgroups [15, 16]. The established risk factors for the development of severe hyperbilirubinemia in infants ≥35 weeks of gestation include the onset of jaundice in the first 24 hours of life; gestational age 35–36 weeks; blood group incompatibility with positive direct antiglobulin test or another hemolytic disease such as G-6-PD deficiency; predischarge total serum bilirubin in the high-risk zone as per hour-specific nomograms; exclusive breastfeeding; cephalhematoma or significant bruising; and sibling with a history of phototherapy and East Asian race [27]. The emerging data from low-resource settings indicate a need for a better understanding of neonatal hyperbilirubinemia in terms of prevention, etiological evaluation, and management, especially in rural or distant areas of developing countries such as India. There is scope for improved obstetrical and neonatal care at primary and secondary healthcare levels to reduce the burden of neonatal problems, including hyperbilirubinemia and asphyxia as preventable causes of DCP.

Clinical Characteristics

DCP is subcategorized into dystonic and choreoathetosis types based on the semiology of the associated movement disorder. The proportion of the two subgroups in the large registry-based studies has been 70% dystonic and 25–30% choreoathetosis or hyperkinetic [7, 28]. A higher proportion of children with dystonia (80–90%) has been seen more in recent studies, which may be contributed by changes in definitions and awareness of dystonia features rather than a true change in prevalence [15, 18]. The major problems are global developmental delay (93%), abnormal twisting postures (59%), hearing impairment (23%), and speech difficulties (15%) [15, 16]. Clinically, children with DCP have a characteristic dichotomy between the acquisition of motor and cognitive milestones, and this motor-predominant delay is seen significantly more in the hyperbilirubinemia group than in perinatal asphyxia [15, 16].

There is a dearth of studies using validated measures of motor disability in children with DCP from low-resource settings. In our previous study, we ascertained that more than 80% of children with DCP have a severe motor disability and are nonambulant (levels V and IV), irrespective of the etiology. However, independent ambulation was not seen in any child with DCP [15, 16]. Data from Swedish registries that indicate 79% of dyskinetic children remain nonambulatory (21% at level IV and 58% at level V) [18]. In contrast to low-resource settings, the proportion of mild motor disability is higher in the resource-rich settings (20–30%) [17, 18], probably due to early detection and early intervention programs in most developed countries. Children with choreoathetosis achieve better motor milestones than those with predominant dystonia, and the latter subgroup needs early and aggressive rehabilitation [7, 20].

Specific assessment of primary dystonia has been most reliably done by the Barry Albright Dystonia scale and the earlier used Burke-Fahn-Marsden dystonia rating scale [29, 30]. However, the applicability of these scales for younger dyskinetic children with secondary dystonia is not fully known. Hence, there are only a few comparable studies available [15, 18]. Higher dystonia scores are seen with increasing levels of

motor disability (levels IV and V of the Gross Motor Function Classification System) and with the hyperbilirubinemia subgroup [15, 16]. Status dystonicus is a neurologic emergency in children with severe dystonia, and CP is the most common underlying etiological factor [13]. Worsening dystonia predisposed children with DCP to the risk of status dystonicus and further impairs the care and quality of life. Though the interest in DCP is rising, however when compared with spastic CP, the assessment and treatment of patients with dyskinesia is still underreported, given the complexity of dystonia, the difficulty in measuring it, and the lack of consensus definition [31].

Radiological Presentation

Two distinct neuroradiological patterns have been identified in children with DCP, based on the predominant pattern of injury [32, 33]. Typically, children with chronic bilirubin encephalopathy show a bilateral signal change in the globus pallidum, subthalamic nucleus, and substantia nigra. Bilateral symmetric hyperintense signal change in globus pallidum has been considered a marker of severe neonatal indirect hyperbilirubinemia [33, 34]. The subthalamic nucleus hyperintensity in kernicterus may disappear in later scans of term infants, but if present, it may identify the underlying injury [35]. On the contrary, children with DCP due to perinatal asphyxia show bilateral signal changes in the putamen (posterior tip to the posterior half), thalamus (ventrolateral to the entire central area), and periventricular white matter [15]. The higher proportion of periventricular white matter changes in dyskinetic children with perinatal asphyxia is possibly ischemic lesions. Though these are sensitively revealed on MR imaging, they may not play a significant role in the motor problems of children with DCP [20].

There is a dearth of large studies with clinical-radiological correlations in DCP [4]. Most of the information is based on small case series or cohorts of specific etiological subgroups. The larger population-based studies are underrepresentative of the dyskinetic population [6], and hyperbilirubinemia has not been seen in most of them [4, 18]. Magnetic resonance imaging scans were reported as showing basal ganglia and/or thalamus changes in 52% overall; over half of these were CT scans and no clinical-radiological correlation has been provided [18]. Our studies in children with CP and DCP highlight important radiological findings in a limited cohort of patients [9, 15, 16]; however, larger population-based multicentric studies are needed to assess the pattern of motor injury in these patients, using newer sophisticated MRI techniques.

Conclusion

There are challenges to diagnosing and managing DCP in developing countries. The variable tone of DCP often overlaps with spasticity and the inability to clearly distinguish one from the other, often leading to an incorrect diagnosis of the "mixed phenotypes." The disabling comorbidities often mask the true assessment of the severity of dystonia. Correct identification is important, as several conditions that mimic generalized dystonia, such as neurometabolic disorders, can present in the same age group. The clinical and radiological features, type, and severity of comorbidities of the DCP group are different from the children with other types of cerebral palsy. There is also a felt need for the establishment of patient registries in low-resource settings for better characterization of large population-based data. This can begin by local pediatric neurology experts and centers collaborating to collate information on specific aspects of the disorder and then projecting these baseline data to the funding agencies to start nationwide registries. Such information will help identify the preventable causes prevalent in the region and will also help in initiating policy changes to mitigate these factors.

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Conflict of interest

None.

Author contributions

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