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Cerebral palsy in the genomic era: Metabolic/genetic movement disorders mimicking cerebral palsy

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Abstract

Cerebral palsy (CP) is a heterogeneous neurodevelopmental disorder primarily characterized by motor impairment caused by non-progressive disturbances in the developing brain. While traditionally thought to be linked to perinatal and environmental factors, recent research has emphasized the role of genetic contributions in the development of CP. Advances in genomic technologies, such as next-generation sequencing, have identified associations with de novo mutations, single-gene disorders, and structural chromosomal variations. These findings challenge the traditional view of CP as solely acquired and highlight its genetic complexity. This review explores the genomic underpinnings of CP, discussing the implications of recent discoveries for diagnosis, treatment, and future research in personalized medicine.

Keywords: Cerebral palsy, Metabolic diseases, Genetic disieases, Next generation sequencing, Mimics.

Introduction

Cerebral palsy (CP) is a well-known, physically disabling condition describing a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain [1]. The motor disorders of CP are often accompanied by intellectual disability, epilepsy, and behavior problems, rendering it a heterogenous condition. The classification of types of CP is based on clinical features and predominant neurological findings. Three main groups have been identified: spastic, dyskinetic, and ataxic CP [1]. Other motor disorders such as muscle weakness, hypotonia, or impaired selective movements can be observed across the range of presentations and along the lifespan. Aberrations of many different genetic loci can produce a CP phenotype [2]. Recognizing the cause of CP in an affected patient is essential to providing optimal clinical management, including precision therapy.

Pediatric movement disorders consist of a heterogeneous group caused by numerous neurological diseases. Whereas hypokinetic disorders, including parkinsonism, predominate in adults, children more commonly demonstrate hyperkinetic disorders such as tics, tremor, chorea, and dystonia [3]. Different neurological disorders in children share overlapping movement disorders making a diagnosis of the underlying cause of the movement disorder challenging. There are a large number of genetic and neurometabolic diseases that cause secondary movement disorders in childhood. Their clinical presentation can meet the diagnostic criteria of CP, particularly at early age [4]. Early detection of treatable inborn error of metabolism allows for timely interventions to prevent disease progression and irreversible central nervous system damage and, in some cases, to improve neurological functioning. Detection of an inherited metabolic/genetic disease for which no treatment currently exists allows for counseling of the affected families, improved management of comorbidities, and provides the essential stepping stone for future research [5].

Selected Disorders With Prominent Dystonia and/or Chorea

Table 1 summarizes the main inherited metabolic/genetic diseases with movement disorders presenting as mimickers of CP.

Dyskinetic CP is the second most common type of CP after spastic forms, typically caused by non-progressive lesions to the basal ganglia or thalamus, or both. In dyskinetic CP, two major movement disorders, dystonia and choreoathetosis, are present together most of the time. Dystonia is often more pronounced and severe than choreoathetosis [1].

A number of inherited metabolic and genetic diseases may present with dystonia [5–7]. For example, monoamine neurotransmitter disorders, glucose transporter deficiency type 1, cerebral creatine deficiency syndrome, or Lesch-Nyhan syndrome can mimic dyskinetic CP. These genetic causes of dystonia can be misdiagnosed with CP because of the nonprogressive nature of the motor manifestations. There are, however, characteristic clinical features in this group of disorders that should prompt their suspicion. The presence of oculogyric crises, diurnal

Table 1. Genetic/metabolic disorders with prominent dyskinesia

– Dopa-responsive dystonia
– Sepiapterin reductase deficiency
– L-Amino acid decarboxylase deficiency
– Glutaric aciduria type 1
– Glucose transporter deficiency type 1
– Neurodegeneration with brain iron accumulation
– Cerebral creatine deficiency syndrome
– Lesch Nyhan syndrome
– Cerebral folate deficiency
– ADCY5-related dyskinesia
– PCDH12-related dyskinesia
– NKX2-1 related ataxic dyskinetic CP
– TSEN54 Gene-related pontocerebellar hypoplasia

variation of the symptoms, or a marked exacerbation of motor symptoms late in the day and/or improvement with sleep, indicate a monoamine neurotransmitter disorder. Regarding glucose transporter deficiency type 1, worsening of symptoms with fasting or exercise is a good diagnostic clue [5–7].

Depending on the specific condition, treatment may include variable combinations of supplementation with the cofactor, tetrahydrobiopterin (BH4), levodopa, and 5-hydroxytryptophan for several monoamine neurotransmitter disorders, ketogenic diet for glucose transporter deficiency type 1, or creatine supplementation for cerebral creatine deficiency [5–7]. In glutaric aciduria type 1, glutaric acid is neurotoxic and may cause permanent dystonia and other neurological sequalae. Aggressive diet treatment prevents injury to the brain.

Selected Disorders With Ataxia and Mixed Motor Features

Table 2 summarizes the main metabolic/genetic movement disorders presenting as ataxic CP.

Up to 10% of children with CP are diagnosed with the ataxic type [1]. Isolated ataxia is a rare finding in patients with CP associated with perinatal brain injury. Therefore, investigation for genetic causes of ataxia should be strongly considered in any patient who presents with predominant ataxia, especially in the context of normal brain imaging. Indeed, early-onset ataxia can signal a host of genetic disorders that are often progressive (thus not CP) with poor outcomes. For example, ataxia-telangiectasia, spinocerebellar ataxia, coenzyme Q10 deficiency, and Joubert syndrome can mimic ataxic CP in early life [5–7].

"Red Flags" When Reviewing a Child With CP

Table 3 summarizes the clinical and neuroimaging features that should alert the physician to a possible underlying metabolic or genetic disorder presenting with movement disorder that mimics CP. Thorough history and a careful neurological examination

Table 2. Genetic/metabolic disorders with prominent ataxia

– Coenzyme Q10 deficiency
– Glucose transporter deficiency type 1
– Ataxia telangiectasia
– Pelizaeus-Merzbacher disease
– Hereditary ataxias
– Joubert syndrome
– Mitochondrial cytopathies
– Pontocerebellar hypoplasia
– Cockayne syndrome
– Niemann-Pick disease type C
– Angelman syndrome
– Gangliosidosis type 1, juvenile and adult forms
– Non-ketotic hyperglycinemia
– Maple syrup urine disease
– NKX2-1 related ataxic dyskinetic CP

Table 3. 'Red Flags' when reviewing a child with CP

– No risk factors for CP such as: prematurity, low birthweight, multiple births, hypoglycemia, jaundice and kernicterus, intrapartum asphyxia, intracranial hemorrhage, infection, stroke, or head injuries
– Positive family history of CP
– Fluctuation in motor symptoms
– Paroxysmal symptoms in relation to time of day, diet/fasting, or activity
– Progressive neurological symptoms
– Regression of milestones
– Isolated motor dysfunction such as isolated ataxia or isolated hypotonia without dystonia or spasticity
– Eye movement abnormalities (e.g., oculogyria, oculomotor apraxia, or paroxysmal saccadic eye-head movements)
– Normal neuroimaging
– Nonspecific abnormalities, such as isolated globus pallidus involvement, which can suggest methylmalonic aciduria

are essential in the evaluation of a patient suspected to have CP. The utility of next-generation sequencing in the clinical field has been widely demonstrated in different groups of diseases, mainly in metabolic/genetic movement disorders. Those metabolic and genetic movement disorders may present with various phenotypes, some of them resembling CP. The first approach should be based on the history, clinical examination, and neuroimaging findings. Brain MRI is estimated to be abnormal in 70–90% of children with CP. Normal brain MRI or atypical brain MRI abnormalities should therefore raise the question of an alternative diagnosis. In a dystonic or ataxic child with no risk factors (adverse events around delivery; e.g., hypoxia or bilirubin encephalopathy) and a normal MRI scan of brain and spine, it is important to consider other causes of dystonia or ataxia (genetic and metabolic) [5–7].

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