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## Clinical and biochemical footprints of inherited metabolic disease. V. Cerebral palsy phenotypes

Gabriella Horvath<sup>1</sup>, Nenad Blau<sup>2</sup>, Carlos Ferreira<sup>3</sup>

<sup>1</sup>Department of Pediatrics, Division of Biochemical Genetics, University of British Columbia, BC Children's Hospital, Vancouver, BC, Canada

<sup>2</sup>Division of Metabolism, University Children's Hospital Zürich, Zurich, Switzerland

<sup>3</sup>National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA

### Abstract

Cerebral palsy is the most common physical disability of childhood describing a heterogeneous group of neurodevelopmental disorders that cause activity limitation, but often are accompanied by disturbances of sensation, perception, cognition, communication and behavior, or by epilepsy. Inborn errors of metabolism have been reported in the literature as presenting with features of cerebral palsy. We reviewed and updated the list of metabolic disorders known to be associated with symptoms suggestive of cerebral palsy and found more than 150 relevant IEMs. This represents the fifth of a series of articles attempting to create and maintain a comprehensive list of clinical and metabolic differential diagnosis according to system involvement.

### Keywords

Cerebral palsy; Inborn errors of metabolism; Developmental delay; Motor developmental delay; Developmental regression; Spasticity; Extrapyramidal movement disorder; Ataxia; Hypertonia

## 1. Introduction

This is the fifth in a series of articles that aim to provide a comprehensive list of inherited metabolic diseases associated with specific signs and symptoms. The first four issues of the clinical and biochemical footprints were dedicated to inborn errors of metabolism (IEMs) associated with movement disorders [1], metabolic liver disorders [2], those with psychiatric

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Correspondence: Gabriella Horvath, Department of Pediatrics, Division of Biochemical Genetics, University of British Columbia, BC Children's Hospital, 4480 Oak Street, Vancouver, BC, V6H 3V4, Canada, gabriella.horvath@cw.bc.ca.

#### Disclosures

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presentations [3] and those associated with cardiovascular involvement [4]. These articles provide a rapidly accessible list that serve as an updated metabolic differential diagnosis for clinicians.

The list follows the classification utilized in the knowledge base of inborn errors of metabolism (IEMbase) [5], the Nosology of inborn errors of metabolism (IEMs) [6] and the International Classification of Inherited Metabolic Disorders (ICIMD) [7].

## 2. Definitions

Cerebral palsy (CP) is a well-known physically disabling condition. It affects between 2 and 3 per 1,000 live births, and is thought to be the most common cause of serious disability in childhood (Surveillance of Cerebral Palsy in Europe 2000) [8]. CP describes 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. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, and behavior, by epilepsy and by secondary musculoskeletal problems [9]. The general agreement is that CP is a heterogeneous condition in terms of etiology, severity and types of impairments. Commonly reported comorbidities include intellectual disability in 30–65%, seizure disorders in 30–50%, speech and language deficits in 40%, visual impairments in 40% and hearing problems in 5–15% of patients [10]. It disrupts the normal process of development in childhood, and it is a permanent condition, but it can have changing pattern of manifestations over time. Neurodevelopmental disabilities that do not primarily affect movement and posture are not considered CP. A child who has severely impaired cognition and no motor signs is not considered to have CP. The term non-progressive is used to denote that the pathophysiological mechanisms leading to CP are presumed to arise from a single inciting event or a series of events which are no longer active. This event can still cause changing clinical manifestations over time [9].

## 3. Classification

The classification of CP is made according to the motor abnormalities (tone and movement disorders – spasticity, ataxia, dystonia, athetosis), the accompanying impairments (seizures, hearing, vision impairments, attention, behavior or cognitive deficits), the anatomical and neuro-imaging findings, and the causation and timing.

The understanding of developmental neurology, including genetic and biochemical influences on brain development, is increasing rapidly, but the full understanding of causal pathways and mechanisms leading to CP remains elusive.

## 4. Genetic causes of CP

Prior to investigating genetic causes of CP, the most common causes were attributed to isolated, or a combination of prenatal, perinatal and postnatal risk factors, such as prematurity, birth asphyxia, low birth weight, multiple pregnancy, coexisting congenital anomalies, fetal intrauterine infection, maternal infection during labor, or placental

pathology [11–13]. The International Cerebral Palsy Task Force published a list of three essential and five non-essential criteria to define an acute intrapartum hypoxic event, with the absence of any of the essential criteria strongly suggesting that CP was not caused by intrapartum hypoxia. The essential criteria include evidence of metabolic acidosis in fetal or neonatal blood and early onset of neonatal encephalopathy. In the nonessential criteria the Task Force includes evidence of an intrapartum hypoxic event, such as low fetal heart rate, low Apgar scores, multisystem presentation and early imaging abnormalities [14].

In recent years, the improved and more widely available genetic testing, have allowed an alternative hypothesis of rare genomic abnormalities causing many of the neurodevelopmental disorders, such as intellectual disabilities and autism. Previous studies based on familial forms of CP estimated that genetic variants causing CP account for about 2% of cases [15]. With the advent of affordable next generation sequencing, more genetic causes are identified, increasing this number to anywhere between 14% to 45–60% [10,16,17]. A recent study by Moreno-de-Luca studying a large cohort of pediatric and adult patients with CP, found the yield for molecular diagnosis between 10.5–32.7%, depending if patients were ascertained through a health-care based cohort (adult patients), or were from clinical laboratory referral (pediatric patients) [18]. Several monogenic disorders often present with clinical manifestations of cerebral palsy. These include several non-syndromic genetic disorders and inborn errors of metabolism. Although individually rare, these disorders are collectively common, and should be entertained when evaluating someone with the diagnosis of CP, especially since some can be treated successfully if diagnosed in early life (i.e., dopa-responsive dystonia caused by *GCHI* pathogenic variants and bipterin deficiency disorders).

Early genetic studies identified a few genes that can cause idiopathic cerebral palsy, such as *GADI*, *KANK1*, *AP4MI*, *AP4E1*, *AP4B1*, and *AP4S1* [19–22]. With the introduction of exome sequencing (ES) more genetic causes have been found, with variable yield of a positive diagnosis. MacLennan et al. reported a 14% yield for likely pathogenic variants while investigating 98 cases with trio-ES and finding genetic variants in 57 cases. They also described 8 novel genes in CP, 5 known genetic diseases with CP as a new phenotype, and another 44% with genetic variants of lesser bioinformatic priority [16]. Schnekenberg et al. investigated seven patients with ataxic CP, using trio-ES and identified *de novo* mutations in four, associated with advanced paternal age, in three different genes, *KCNC3*, *ITPR1* and *SPTBN2* [23]. Kruer et al. added *ADD3* as a cause of spastic CP [24]. Furthermore, several genes causing Spastic Paraplegia have been implicated in inherited forms of CP, such as *NIPA1* (SPG6), *SPAST* (SPG4), and *SPG34* [25] [21]. A study done by Takezawa et al. in 2018 analyzed trio-ES in 17 patients with CP and no specific MRI findings, and found pathogenic/likely pathogenic variants within eight genes: *CTNNA1*, *CYP2U1*, *SPAST*, *GNAO1*, *CACNA1A*, *AMPD2*, *STXBPI*, and *SCN2A* [26]. In the most recent publication by Moreno-de-Luca, the following genes were found to be present in both pediatric and adult patients with CP: *MECP2*, *TCF4*, *TUBA1A*, *SLC2A1*, *KMT2A*, *CAMTA1*, *ATL1*, *IQSEC2*, *ASXL3* and *LICAM* [18].

Large next generation sequencing studies have done network analysis and identified enrichment of Rho GTPase, extracellular matrix, focal adhesion and cytoskeleton pathways.

In the ES analysis of 250 parent-offspring trios, Jin et al. estimated that 14% of cases could be attributed to an excess of damaging *de novo* or recessive variants, providing evidence for genetically mediated dysregulation of early neuronal connectivity in CP [27].

Leach et al. did a systematic review of the literature for treatable inborn errors of metabolism (IEM) presenting as CP, identifying all reports of IEMs presenting with CP symptoms before 5 years of age. They have identified 54 treatable IEMs belonging to 13 different biochemical categories. For 26 of these IEMs, a treatment is available that targets the primary underlying pathophysiology (e.g., neurotransmitter supplementation) and for 41 treatment is available to stabilize/prevent metabolic crisis [28]. Matthews et al. in 2019 reported the result of trio-ES in 49 probands presenting with atypical CP and found a molecular diagnosis in 65% of patients [29]. Patients considered eligible, had to have impaired motor function with onset at birth or within the first year of life and one or more of the following: severe intellectual disability, progressive neurological deterioration, other abnormalities on neurological examination, multiorgan disease, congenital abnormalities outside the nervous system, an abnormal neurotransmitter profile, family history, or brain imaging findings not typical for CP. The high diagnostic rate in this study can be explained by focused recruitment and strict inclusion criteria. A few other reviews have tried to present a list of neurogenic disorders causing CP, such as Lee et al. 2014, or focusing on IEMs and Hakami et al. 2019 [30] [31], but no comprehensive review and differential diagnosis in inborn errors of metabolism has been attempted before. We have done a systematic review of IEMbase and found 151 diseases that lead to CP presentation. We have summarized the most updated list of differential diagnosis of IEMs presenting with symptoms suggestive of CP in Suppl. Table 1. The relative occurrence rates of the most common symptoms associated with 151 IEMs presenting with CP phenotype, is represented as a heat map of the major motor symptoms in Figure 1.

## 5. Signs and symptoms

We categorized the signs and symptoms in two groups of disorders:

1. Developmental delay/motor/psychomotor
2. Developmental regression with motor problems; since CP by definition encompasses only permanent/non-progressive disorders, only conditions where regression starts early were included, as exact clarification of regression may not always be easy at this age in the clinical setting

All categories had as presenting symptoms predominant motor signs: ataxia, extrapyramidal signs and/or spasticity.

Only conditions with age of presentation in the first 2 years of life were included.

In the category of developmental delay/motor/psychomotor retardation there were 22 conditions identified to present with ataxia as the isolated motor finding, 12 with isolated extrapyramidal disorders and 37 with only spasticity. Sixty-eight conditions can present with some combination of these three. In the last category of developmental regression there were 6 conditions presenting with some combination of the presenting movement disorder, 1 with isolated ataxia and spasticity each and 2 conditions with isolated extrapyramidal disorder

(Suppl. Table 1). Given that in category 2 there were very few disorders, for the analysis of the percentage of occurrence of symptoms associated with CP phenotypes we combined the 2 categories into a single category of “developmental delay/impairment/regression”, separating them into ataxia, pyramidal signs and spasticity (Fig 1, Suppl. Table 1).

## 6. Diagnosis and differential diagnosis

With the recent advances in genomic analysis in CP and the growing number of IEMs that have specific treatment options, an inherited metabolic disease should be suspected and ruled out in patients presenting with CP phenotype, especially if the criteria for hypoxia are not met. Red flags should be all symptoms and signs that are not in concordance with the aforementioned essential or non-essential criteria for intrapartum hypoxia.

A list of laboratory investigations to aid in the diagnosis of the various listed IEMs is summarized in Table 1. Only 21 conditions out of the 151 can be solely diagnosed through genetic testing.

## 7. Treatment

It is of utmost importance to make a diagnosis of IEM in patients with CP, because some of these conditions may have treatment that could be considered curative, for example L-dopa therapy in most of the bipterin deficiencies, including dopa-responsive dystonia, caused by autosomal dominant or recessive *GCHI* pathogenic variants. Other conditions may have treatment that significantly alter the course of the disease, either with specific dietary manipulation or with avoidance of acute metabolic crises (disorders of ammonia detoxification, disorders of sulfur amino acid and sulfide metabolism, branch-chain aminoacidopathies, disorders of serine and glycine metabolism, cobalamin disorders, disorders of folate and copper metabolism, pyruvate metabolism, and ketone body metabolism). Some conditions have gene therapy available, such as AADC deficiency. Also, through constant research, new therapies are developed regularly. Supplemental Table 1 includes information on primary treatment options for the list of IEMs. Finding a specific etiology, such as a diagnosis of IEM in patients diagnosed with CP is helpful in genetic counseling, especially if familial cases are present, prevent birth of a similarly affected sibling, but would also end a diagnostic odyssey and help clear any feeling of guilt in parents or health professionals involved in the delivery.

## 8. Conclusions

In this fifth issue from a series of educational summaries providing a comprehensive and updated list of metabolic differential diagnosis according to system involvement, we focus on IEMs presenting with CP signs and symptoms. We provide a comprehensive differential diagnosis, standard laboratory diagnostic methods and treatment approaches. The full list can be accessed at [www.iembase.org/gamuts](http://www.iembase.org/gamuts).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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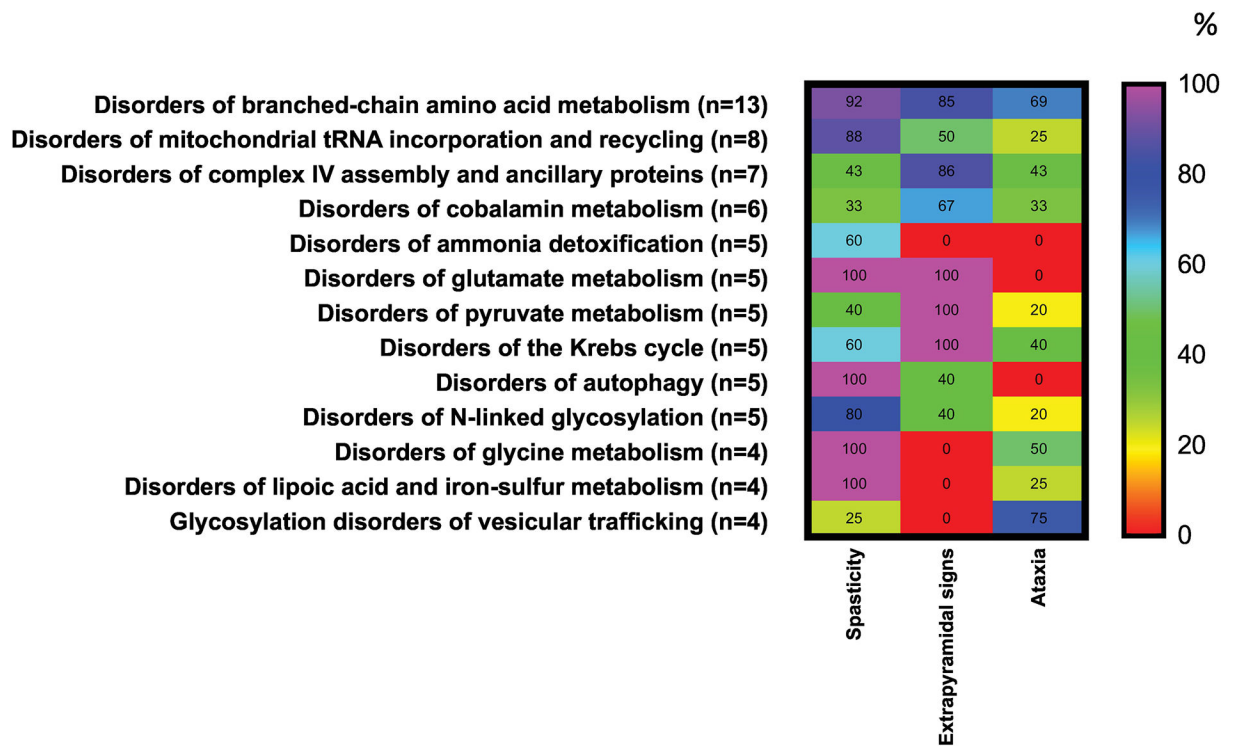
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**Figure 1.**

Occurrence (%) of spasticity, extrapyramidal signs or ataxia in a combination with developmental delay or impairment or regression in 13 categories of IEMs. The percentages for neurological involvement were calculated using as the denominator the total number of IEMs in each category presenting with spasticity, extrapyramidal signs or ataxia. Heat scale ranges from red (0%) for diseases with no particular symptoms reported to violet (100%) for diseases with particular symptoms occurring with highly frequency. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

**Table 1.**

Biochemical investigations in cerebral palsy.

Basic tests	Profiles	Special tests
Ammonia (B)	Acylcarnitines (DBS, P)	Copper(S, U)
ASAT/ALAT (P)	Amino acids (P, U)	Ceruloplasmin (S)
Blood count	Lipid panel (S)	Carnitine (P)
CK (P)	Biogenic amines (CSF)	Lysosomal enzyme activity
Coagulation factors	Organic acids (U)	(WBC, FB)
Glucose (P)	Pterins (CSF)	Glutathione (RBC)
Lactate (P)	Sialotransferins (S)	Interferon-alpha (CSF)

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