The Expanding Role of Genetics in Cerebral Palsy

Lisa T. Emrick, MD[a,b,*], Shannon M. DiCarlo, MD[c,1]

KEYWORDS

• Cerebral palsy • Genetics • Exome sequencing

KEY POINTS

- Cerebral palsy is a descriptive term for patients with nonprogressive motor impairments, typically thought to be associated with specific brain imaging abnormalities but now often inclusive of patients with nonprogressive genetic disorders.
- Patients with atypical presentations of cerebral palsy (normal head imaging, progressive course, family history of similar symptoms) should be considered for further genetic work-up.
- Genetic evaluation should be pursued in a stepwise fashion in order to maximize diagnostic yield with an emphasis on treatable disorders and to minimize costs.
- A genetic diagnosis may provide specific treatments for patients and reoccurrence risks to families.

INTRODUCTION

Cerebral palsy is a clinical diagnosis of a nonprogressive developmental disorder of motor impairment.[1] It was previously thought to be related to brain injury or a developmental brain malformation but the scope of the diagnosis of cerebral palsy has been broadening significantly in recent years to include patients with genetic disorders. The advent of novel genetic testing has been able to give patients who previously had a vague diagnosis of presumed or so-called MRI-negative cerebral palsy a more specific cause.

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[a] Division of Neurology and Departmental Neurosciences, Department Pediatrics, Baylor College of Medicine, Houston, TX, USA; [b] Department of Human and Molecular Genetics, Baylor College of Medicine, Houston, TX, USA; [c] Division of Neurology and Departmental Neurosciences, Department Pediatrics, Cerebral Palsy Clinic, Baylor College of Medicine, Houston, TX, USA

[1] Present address: 15400 Southwest Freeway Suite 200, Sugarland, TX 77478.

* Corresponding author. 6701 Fannin Street, Suite 1250, Houston, TX 77030.

E-mail address: ltemrick@texaschildrens.org

Twitter: Lemrick444 (L.T.E.)

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There is more attention on genetic causes for cerebral palsy, and previous articles quote a range from 30%[2] to approximately between 70% and 80% of cerebral palsy attributed to perinatal causes are secondary to a genetic cause.[3] Previous literature focused on cerebral palsy masqueraders[4] and there has been an expansion as well as overlap of phenotypes of conditions with the discovery of new genes. At the time of writing, there are more than 800 genes in the Online Mendelian Inheritance in Man (OMIM) database available online at https://www.omim.org associated with cerebral palsy, representing more than 900 clinical conditions.

This article helps clinicians to determine what patients would benefit from a more thorough genetic/metabolic evaluation and helps to delineate an approach for the work-up, with an emphasis on newer technologies and the evolving fields of fetal medicine and genetics. It is not meant to be an exhaustive list of genes and conditions related to cerebral palsy but provides guidance to providers to assist in clarifying a cause for some patients' symptoms.

CEREBRAL PALSY

A Brief Definition

Cerebral palsy is a phenotypic description that includes any patient who has a nonprogressive but evolving motor impairment. The motor impairment was previously thought to be secondary to a lesion or anomaly in the brain that occurs early in development but now includes developmental brain disorders that appear structurally normal on neuroimaging. Although the disorder itself is not progressive, the clinical expression may change over time as the brain matures. Patients with cerebral palsy sometimes have associated symptoms including but not limited to disturbances in sensation, cognition, communication, perception, or behavior, and possibly including a seizure disorder.[5]

Common Risk Factors

Risk factors that predispose individuals to cerebral palsy are often divided into groups based on timing: preconception (maternal), prenatal, perinatal, and postnatal (**Table 1**).

Table 1
Risk factors for cerebral palsy

Maternal	Prenatal	Perinatal	Postnatal
• Epilepsy • Thyroid disease • Advanced maternal age • Low socioeconomic status • Smoking • Intellectual disability • History of premature delivery • History of multiple miscarriages	• Placental abnormalities • Poor fetal growth • Cardiac anomalies • Maternal disease during pregnancy (eg, diabetes, thyroid disease, epilepsy) • Poor prenatal care • High or low amniotic fluid level • Preeclampsia • TORCH infections • Chorioamnionitis • Twin gestation	• Prolonged delivery • Traumatic delivery • Breech presentation • Meconium • Fetal hypoxia • Low APGAR scores • Seizures • Infection • Low blood sugar • Jaundice	• Stroke • Abusive head trauma • Meningitis

Abbreviations: APGAR, appearance, pulse, grimace, activity, and respiration; TORCH, toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B_{19}), rubella, cytomegalovirus, and herpes.

From DiCarlo S, Schwabe A. Cerebral palsy and static encephalopathies. In: Kline MW, editor. Rudolph's pediatrics. 23rd edition. New York: McGraw-Hill; 2018. p. 2672–5; with permission.

If the damage to the brain occurs after age 3 years, an alternate diagnosis is given because the spectrum of symptoms can be different when changes occur in a more developed brain.

Typical Work-up

In patients who present with a clinical picture concerning for a diagnosis of cerebral palsy, a thorough history and physical is first performed. Special attention needs to be paid to prenatal and birth history, timing of onset of symptoms, and any history of developmental plateaus or regressions. Prenatal medicine is evolving and detection of central nervous system abnormalities with the development of more sensitive fetal ultrasonography and fetal MRI is increasing as well as prenatal genetic testing.[6,7]

A family history is also important to help assess the risk of an inherited genetic condition. If possible, obtaining a 3-generation pedigree is recommended, especially if considering sending broad genetic tests such as exome or genome sequencing in order to provide the family with the most informative test results. **Table 2** provides questions suggested to ask when obtaining a family history. Genetic counselors are key members of the multidisciplinary team to help obtain thorough histories and pedigrees as well as to provide families with both pretest and posttest counseling of genetic tests.

The physical examination should include a particular focus on the neurologic and musculoskeletal components of the examination. The physical examination should also include the presence or absence of dysmorphic features that could indicate syndromic causes for patients to have abnormal tone.

If the history and examination indicate a patient with a central cause for the symptoms, imaging studies are then performed (if not done already). Some patients have imaging performed before arriving in clinic and this does not need to be repeated if it shows findings in congruence with the patient's symptoms and history. The preferred study, if one has not been done, is MRI brain without contrast, although this often requires sedation.

Once history, examination, and imaging are performed, if findings are consistent with the clinical picture, no further work-up is indicated to establish a diagnosis of cerebral palsy. The type of cerebral palsy is then classified (eg, quadriplegic, hemiplegic, diplegic, ataxic), which helps to more easily communicate the patient's diagnosis to other providers. Associated conditions are then screened for (eg, developmental delay/intellectual disability, ophthalmologic/hearing impairments, speech/language delay, feeding/swallowing dysfunction, and/or clinical events concerning for seizures) and evaluation for those conditions is performed as indicated.

Why Consider Genetic Studies?

Patients with normal MRI or other red flags listed may need further genetic work-up (**Box 1**). Patients with abnormal MRI with evidence of a developmental malformation should be evaluated for a genetic or acquired cause of a migrational abnormality. Acquired causes for migrational anomalies can include TORCH (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B_{19}], rubella, cytomegalovirus, and herpes) infections and in utero ischemia. MRI abnormalities that are found without a typical history (eg, a completely normal pregnancy and birth with findings of hypoxia on MRI) should also have further studies performed.

The main focus of this article is genetic causes that mimic cerebral palsy. However, there is an emerging area in discussing the utility of genetic testing in patients with risk factors for cerebral palsy, such as prematurity, migrational anomalies, or hypoxia.[2] Genetic testing is indicated if there is the presence of other risk factors such as a

Table 2
Relevant questions in obtaining a family history

Question	Genetic Testing Implications	Genetic Test
Is there a family history of similar motor delay?	Autosomal dominant conditions such as hereditary spastic paraparesis, dopa-responsive dystonia	Focused testing based on family history
Is there a family history of other neurodevelopmental disorders?	Neurodevelopmental condition with phenotypic heterogeneity	Focused testing based on family history
Is there a possibility of shared ancestry between parents?	Consanguinity increases risk for at least 1 if not more than 1 autosomal recessive condition	SNP-based chromosomal microarrays can detect chromosomal regions of loss of homozygosity Prefer broad sequencing testing such as whole-exome or whole-genome sequencing based on risk for multiple recessive disorders
If there is a family history of multiple miscarriages?	May be an increased risk for a chromosomal anomaly that may be secondary to an unbalanced translocation in patient	Chromosomal testing: chromosomal microarray to detect microdeletions or duplications plus karyotype to check for a translocation Karyotype in parents to detect balanced translocations
Is there a family history of other possible conditions, such as early cancer, stroke, or cardiac conditions?	Possibility of detecting other genetic conditions that may be treatable or medically actionable for the patient Decrease the chance of unsuspected incidental findings if sending exome or genome sequencing	Recommend sending exome or genome sequencing for the most complete genetic testing for the patient based on motor phenotype and family history of other possible dominantly inherited condition

Abbreviation: SNP, single nucleotide polymorphism.

suspicious family history for other affected family members, MRI findings inconsistent with the patient's clinical presentation, or the presence of other congenital anomalies.[2]

Making a genetic diagnosis can be helpful in many ways, including possible treatment options, discussing inheritance possibilities, and closure for the family. Treatment options can include specific treatment, such as in dopa-responsive dystonia or restricted diet and ammonia scavenging agents for arginase deficiency. There may be more specific treatments, such as enzyme replacement or gene therapy, for some of these conditions, such as spinal muscular atrophy. A genetic diagnosis can aid in guiding prognosis in conditions that were previously thought to be static but may be progressive; for example, a primary mitochondrial disorder or a disorder of brain iron accumulation.

Inheritance is often overlooked by nongenetic providers, but having a genetic diagnosis can help with family planning. If the patient has a genetic condition with an

Box 1
When to look further: red flags

- Normal MRI findings
- Imaging abnormalities isolated to the globus pallidus
- Severe symptoms in the absence of a history of perinatal injury
- Family history pattern of disease inheritance, or consanguinity
- Neurodevelopmental regression, or progressively worsening symptoms
- Isolated muscular hypotonia
- Isolated ataxia
- Rigidity (as opposed to spasticity) on physician examination
- Paraplegia

From Lee RW, Poretti A, Cohen JS, et al. A diagnostic approach for cerebral palsy in the genomic era. Neuromolecular Med. 2014;16(4):821–44; with permission.

autosomal recessive inheritance, there is a 1:4 chance of reoccurrence. If the genetic pathogenic variant (previously referred to as mutation) is known, then parents can consider preimplantation genetic diagnosis (PGD) versus postconception perinatal amniocentesis to test for the familial variants. PGD is a method of in vitro fertilization with selection of embryos without the known familial variant for implantation.[8] A de novo variant (not detected in either parent's blood) has a very low risk of reoccurrence if it occurred randomly in the egg or sperm before conception. There is a slight reoccurrence risk if that pathogenic variant occurs in multiple eggs or sperm secondary to germline mosaicism. It is difficult to define the reoccurrence risk because it depends on how many gametes have the pathogenic variant. The risk can range between 1% and 30% for de novo variants secondary to the possibility of germline mosaicism. It is one of the evolving areas in prenatal genetics. Parents of affected children with a known genetic pathogenic variant can still choose to do prenatal genetic diagnosis for future pregnancies, even if the variant was de novo. However, PGD can be expensive and may not be covered by insurance. Providers can refer parents of children with a suspected or confirmed genetic condition for prenatal genetic counseling for preconception options for family planning.

GENETIC TESTING OVERVIEW

Common Genetic Studies

Variations in the genetic code can lead to disruptions in the functions of the gene. Variations can occur either on a chromosomal level, such as with either microdeletions or microduplications on the chromosome, also known as copy number variants (CNVs), single nucleotide variants (SNVs), or repeat expansions. **Table 3** lists various types of genetic tests with the pros and cons/limitations for detecting these variants.

Microdeletions or microduplications have been reported in patients with diagnoses of cerebral palsy. Previous studies have reported between 10% and 12% detection rate of likely pathogenic CNV in patients with cerebral palsy.[2] The genes included in these CNVs include *KANK1*, *WDR45*, *HSPA4*, and *SPAST*.[2]

Variations can also occur secondary to single DNA nucleotide variants (SNV) that can be detected with DNA sequencing methods, such as Sanger sequencing or next-generation sequencing. Variants are classified as benign, likely benign,

Table 3
Genetic testing options

Genetic Test	Indications	Pros	Cons/Limitations
Karyotype	Specific dysmorphic features History of multiple miscarriages in mother	Trisomies including mosaicism Large chromosomal deletions Balanced chromosomal rearrangement, ring chromosomes	Does not detect microdeletions or microduplications
Chromosome microarray	Dysmorphic features Multiple congenital anomalies Associated developmental delay Nonspecific phenotype	Microdeletions and Microduplications SNP arrays: detect areas of homozygosity and uniparental disomy	Does not detect small deletions, duplications or insertions Does not detect balanced rearrangements or ring chromosomes if balanced, variants of unknown significance
Gene panel/single gene	Specific phenotypes	Better coverage than WES, may be able to detect mosaicism	Limited number of genes
WES	Nonspecific phenotype; specific phenotype but possibility of gene discovery	Broad coverage of genes Medically actionable findings	Variants of unknown significance, incidental findings, does not detect CNVs or repeat expansions
WGS	Nonspecific phenotype; specific phenotype but possibility of gene discovery	Detect single base variant (SNV), microdeletion and duplication, repeat expansions	Insurance coverage Variants of unknown significance, incidental findings
mtDNA	mtDNA-specific conditions	Specific to mtDNA genome	Heteroplasmic difference in blood and other tissues, variants of unknown significance
Repeat Expansion Panels: ataxia panel	Specific disorder	No variants of unknown significance	Limited number of genes if panel or single-gene testing

Abbreviations: mtDNA, mitochondrial DNA; WES, whole-exome sequencing; WGS, whole-genome sequencing.

pathogenic, likely pathogenic, or of unknown significance. The term variants with the qualifying statements ranging from benign to pathogenic replaced the previous terms such as mutations, polymorphisms, and benign variants or mutations secondary to some confusion around the terms and what was benign versus pathogenic.[9] Next-generation sequencing may be used in DNA panels with a specific phenotype, such as neuronal brain iron accumulation disorders. DNA panels can be helpful for specific

phenotypes caused by only a few known genes but has lower detection rates in less specific phenotypes or in conditions with recent gene discovery, such as hereditary spastic paraplegia. Whole-exome sequencing (WES) or whole-genome sequencing (WGS) is recommended for testing in patient with less specific phenotypes, such as hypotonia, or if testing has a low yield from a gene panels such as hereditary spastic paraplegia.[10]

WES is DNA sequencing of the part of the genome that encodes for genes, the exons, and a small portion of the intronic sequences. It covers only about 1% of the genome. WES became clinically available in 2011 and since that time the number of genes associated with a known mendelian disorder has increased from approximately 2000 to 4000 at the end of 2018 and is still increasing. In addition to new genes being discovered, researchers also now see about 4% to 5% of patients undergoing WES who have more than 1 diagnosis,[11] and autosomal recessive conditions may arise from a pathogenic variant in 1 allele and a deletion in the other allele.[12,13] The analysis of WES results also found that there was a higher rate of de novo autosomal dominant conditions that can be detected better when using a trio-based format of sequencing the patient (the proband) and both parents to search for a de novo variant that does not exist in either parent.[13] The detection rate for making a genetic diagnosis is improving with better sequencing methods, more robust genetic bioinformatic programs to analyze the data, and more genes being discovered. However, the detection rates range between 25% and 40%. Genetic testing may show variants of unknown significance that can be difficult to prove to be pathogenic secondary to no functional testing such as a metabolic marker or in vitro assay. Providers can request reanalysis of a patient's previous WES over time or if the patient's symptoms or family history has changed. A reanalysis may lead to a diagnosis if a new gene was discovered since the initial or previous testing or if a variant of unknown significance was reclassified as pathogenic. Other reasons for the lower detection rate include pathogenic variants in noncoding regions, repeat expansions, or small deletions or duplications that may be present but were not detected on the previous testing platforms. It is hoped that the latest platform, WGS will improve the current detection rate. WGS is DNA-based sequencing of both the intronic and exonic sequences of the genome but is not currently at 100% coverage of the genome. WGS is able to detect DNA sequencing variants as well as CNVs and repeat expansions. It is becoming more clinically available by some commercial laboratories in 2019 but is expensive. The costs of testing will decrease over time with the development of newer, faster technologies. Bioinformatic tools to analyze the data will most likely also develop in the coming years to assist with interpreting and storing the data.[14]

Common Metabolic Studies

Inborn errors of metabolism can also mimic all types of cerebral palsy; for example, congenital disorders of glycosylation can present with hypotonia, dopa-responsive dystonias and arginase deficiency can present with spasticity, disorders of hyperhomocysteinuria can present with hemiplegia, and glutaric aciduria or mitochondrial dysfunction can present with dyskinesia. Leach and colleagues[15] provide a comprehensive review of treatable inborn errors of metabolism that can mimic cerebral palsy. The list of treatable disorders is increasing with newer techniques. Many of the disorders can be detected with either screening metabolic tests or, for some, more specific single tests of enzyme function. **Table 4** lists the common screening metabolic tests and disorders associated with specific types of cerebral palsy.

Initial metabolic tests usually include plasma amino acids, acylcarnitine profile, and urine organic acids. Plasma amino acids detect aminoacidurias, urea cycle disorders,

Table 4
Metabolic testing options for cerebral palsy

Cerebral Palsy Type	Metabolic Condition	Metabolic Tests
Spastic diplegia	Arginase deficiency	Plasma amino acids
	Dopa-responsive dystonia	CSF neurotransmitters
	L2 hydroxyglutaric aciduria	Urine organic acids
Spastic quadriplegia	Sulfite oxidase deficiency or molybdenum cofactor deficiency	Urine sulfocysteine, uric acid
	Homocysteinuria, disorders of cobalamin metabolism	Plasma amino acids, homocysteine and acylcarnitine profile, urine organic acids
Extrapyramidal	Glutaric aciduria type 1	Urine organic acids and acylglycines; plasma acylcarnitine profile
	Mitochondrial disorders	Plasma and CSF lactate, plasma and CSF amino acids (alanine), plasma acylcarnitine profile, urine organic acids
Hypotonic	Congenital disorders of glycosylation N and O linked	Serum carbohydrate transferrin include N-glycan and O-glycan analysis
	Aromatic amino decarboxylase deficiency	CNS neurotransmitters

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid.

and some organic acidurias (argininemia, maple syrup urine disease). Acylcarnitine profile is a blood test for fatty acid oxidation disorders (small to large, not very long fatty acids; separate test for X-linked adrenoleukodystrophy and other peroxisomal disorders). The acylcarnitine profile can also assist in diagnosing aminoacidurias and organic aciduria disorders with the assistance of urine organic acid tests. Many of the disorders detected with these initial metabolic screening tests are now detected in the United States as a part of state newborn screening tests.[16] However, newborn screening tests vary by state and have been updated through the years. Therefore, what children have been screened for depends on where they were born and the year they were born.

Additional metabolic testing may be indicated depending on the patient's clinical presentation. Cerebrospinal fluid (CSF) studies can be helpful alone or with comparison of blood samples obtained around the same time to compare ratios for low levels in the CSF.

CSF amino acids and glucose compared with plasma amino acids and glucose tests are indicated if there is the presence of seizures. CSF neurotransmitters are useful if a movement disorder is present with brain MRI that is not consistent with the movements.

MANAGEMENT STRATEGIES

There are different approaches for sending genetic testing in patients with a diagnosis of cerebral palsy. If the patient's clinical history, including family history and neuroimaging, has a specific phenotype, then start with targeted testing based on that phenotype. If the features are nonspecific but there are dysmorphic features or other congenital anomalies or multiple miscarriages in the mother, then a chromosome

microarray is a good test to send. If there is a history of developmental regression, then metabolic testing and an urgent referral to a specialist is recommended. Metabolic testing can also assist in characterizing a patient's phenotype and assist with more specific testing when indicated.

If the patient's phenotype is nonspecific, such as hypotonia, then consider sending a broad test such as WES if spinal muscular atrophy, myotonic dystrophy, and chromosomal abnormalities have been ruled out based on clinical history or negative testing. There are gene panels for many specific phenotypes, such as ataxia, central nervous system migrational disorders, neuromuscular disorders, and treatable disorders. There is a Web site called the Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr), which may be helpful in choosing a panel or a laboratory test to select for genetic testing. The yield of genetic testing is likely to continue to improve with advances in technology such as genomic sequencing and most likely other mechanisms such as mosaic, imprinting, or other multifactorial etiologies that have yet to be discovered. However, functional assays to assist in determining whether a variant is benign or pathogenic continue to lag behind the sequencing technology. One goal for genetic testing in the future will be to have better methods to classify genetic variants as either pathogenic or benign and to decrease the number of variants of unknown significance (VUS).

SUMMARY

Cerebral palsy was once thought to be related to acquired brain injury, but the scope of the diagnosis of cerebral palsy has been broadening significantly in recent years to include patients with genetic disorders. There are more than 800 genetic conditions in the OMIM mendelian genetic database that include cerebral palsy as a part of the phenotype. This number is expected to increase further with the improved methods for expanding the knowledge of the cause of cerebral palsy with growth of fetal medicine and genetics. At present the focus is on genetic conditions that mimic cerebral palsy motor phenotypes; however, there is ongoing work to assist with possibly identifying susceptibility genes for acquired types of cerebral palsy in the future.

DISCLOSURE

The author was a paid consultant for PTC Therapeutics regarding a rare disorder, AADC deficiency.

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