Movement Disorders
CLINICAL PRACTICE

GLUT1 Deficiency in a Patient Diagnosed as Cerebral Palsy: Is NGS a Valuable Tool to Be Considered in All Cases of CP to Detect Underlying Genetic Disorders?

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Cerebral palsy (CP) is defined since 2006 as "a group of permanent disorders of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or immature brain."[1] The prevalence of CP is high, affecting around 2 in every 1,000 live births worldwide.[2] Most CPs have their basis in the pre- or perinatal period and the diagnosis can be challenging in the absence of obvious clinical history predictive of CP, such as neonatal encephalopathy or perinatal stroke.[3] Given that the definition is wide, a lot of neurodevelopmental disorders can resemble CP clinically, and the diagnostic workup that should be applied before attributing a patient's phenotype to a perinatal injury is not well defined. In a review from 2014, the researchers identified no less than 110 inborn errors of metabolism that could mimic CP.[4] This is a very important subject matter, given that some of them are treatable (67 of 110 in the review). Because the age of onset is by definition in infancy or childhood, diagnosis is usually made by pediatricians. However, a lot of these patients are eventually referred to adult movement disorders specialists as they age. The diagnostic efforts are often concentrated within the first years after onset, while the focus rather tends to be on rehabilitation afterward. Diagnosis is made even harder in adulthood, given that information on the potential perinatal injury and the results of childhood investigations are often lacking more than 15 years later. Taking into account the huge progress in medical knowledge and diagnostic tools during the last two decades, we think that the transition from pediatrics to adult neurology may represent a good opportunity to reappraise the diagnosis with a multidisciplinary approach.[5] Dedicated transition care programs in neurology may foster this diagnosis reappraisal.[6]

In the current issue, Ros-Castelló et al. report the case of a 52-year-old woman misdiagnosed as CP, who actually had GLUT1 deficiency.[7] This early misdiagnosis led to considerable diagnosis delay that was highly detrimental to the patient, given that GLUT1 deficiency is a treatable disorder. It is caused by mutations in *SLC2A1* that codes for a glucose transporter, resulting in a cerebral energy deficit. The phenotypic spectrum is wide, ranging from severe encephalopathy manifesting in infancy to isolated paroxysmal exercise-induced dyskinesia occurring later in life.[8] Manifestations can include intellectual deficiency, microcephaly, dystonia, chorea, ataxia, spasticity, and paroxysmal episodes, including seizures and paroxysmal dyskinesia. Worsening with fasting or exercise is a good diagnostic clue. The diagnosis is suggested by low cerebrospinal fluid (CSF) to blood glucose ratio (<0.60) and confirmed by genetic analysis. Standard treatment consists of a ketogenic diet, with a goal of providing alternative energy substrates to the brain. Alternative treatments are however needed, given that the diet is hard to follow. Triheptanoin may be an option, having shown dramatic improvement on paroxysmal dyskinesia in an open-label pilot trial.[9] In the patient reported in this issue, the presence of paroxysmal exercise-induced dyskinesia was a strong clue for the diagnosis.[10] However, that is not always the case because some patients with GLUT1 deficiency do not have paroxysmal episodes (epileptic or nonepileptic) or obvious fasting-induced worsening of their condition. They can present with stable intellectual deficiency and movement disorders, thereby perfectly mimicking CP. As a matter of fact, in our center we just made a diagnosis of GLUT1 deficiency in a 56-year-old patient with mild intellectual deficiency and generalized dystonia, who never had any paroxysmal episodes.

Another treatable disease mimicking CP and not to be missed is dopa-responsive dystonia (DRD). DRD is mostly caused by heterozygous mutations in the GTP-cyclohydroxylase-1 (*GCH1*) gene. It can rarely be caused by autosomal-recessive

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mutations in the tyrosine hydroxylase (TH), sepiapterine reductase (SPR), or pyruvoyl tetrahydropterin synthase (PTPS) genes.[11,12] All these enzymes are required for dopamine synthesis. DRD usually manifests as childhood-onset dystonia with diurnal motor fluctuations, but atypical forms are not uncommon. They comprise adult-onset generalized dystonia, early-onset dystonia that remains focal for decades, paroxysmal exercise-induced dystonia, task-specific dystonia, myoclonic dystonia, isolated parkinsonism very similar to young-onset Parkinson's disease, and spastic paraparesis.[13] Postural tremor, axial hypotonia, and oculogyric crises can be observed. Diagnosis is crucial, given that there is a dramatic response to treatment by low-dose levodopa. A L-dopa trial and/or a CSF neurotransmitter analysis should therefore be proposed in all patients with early-onset dystonia or paroxysmal exercise-induced dyskinesia. It should be noted that brain MRI is usually normal in both GLUT1 deficiency and DRD. That is an important point, given that brain MRI is estimated to be abnormal in 70% to 90% of children with CP.[14,15] Normal brain MRI or atypical brain MRI abnormalities should therefore raise the question of an alternative diagnosis. Other treatable causes of movement disorders that may mimic CP include dystonia/parkinsonism, hypermanganesemia, polycythemia and chronic liver disease, ataxia with vitamin E deficiency, Niemann-Pick disease type C, biotin-thiamine–responsive basal ganglia disease, cerebrotendinous xanthomatosis, and pyruvate dehydrogenase deficiency (Table 1).[16–21]

The diagnostic investigations are rendered difficult by the sheer number of disorders that can mimic CP. One can decide to limit investigations to frequent treatable causes, such as GLUT1 deficiency and DRD, but many rarer causes will be missed by this approach. Even if there is no specific treatment, diagnosis of a genetic disorder is important in order to provide the patient and his or her family with more accurate information on his prognosis and to allow for genetic counseling. Other authors have proposed that brain MRI should be performed in all patients, and that additional investigations should be done in the absence of a definite perinatal injury, or in the presence of a positive family history, symptoms progression, developmental regression, or normal brain MRI.[22] However, clear evidence of perinatal injury is not enough to conclude to a diagnosis of CP, given that the underlying genetic disorder may have made the fetus or newborn more vulnerable to pregnancy or delivery complications.[22]

How many patients with an underlying neurogenetic disorder are misdiagnosed as CP? There is no definite answer, because it has never been systematically studied. One way to answer that question would be to run array comparative genomic hybridization and whole-exome sequencing in a large cohort of patients diagnosed as CP. Without that information, the question remains an open one: Should next-generation sequencing (NGS) be considered in all CP patients? Considering the high prevalence of CP, that would come as a high cost, for a diagnostic yield that may appear disappointing. On the other hand, diagnostic workups conducted in patients before diagnosing CP, which may include metabolic dosages and targeted genetic sequencing, are not without cost. In addition, the economic benefit of a diagnosis of a treatable disorder such as DRD is high, because treated patients with DRD usually live normal lives, without the supportive care required in severe CP.

In the past few years, targeted gene sequencing has been replaced by gene panels for most genetic movement disorders. In the future, the use of NGS will likely be generalized to all patients because its cost will decrease. That will probably be very helpful to avoid misdiagnosing genetic disorders as CP. In the meantime, we believe that every patient with a putative diagnosis of CP should at least undergo a brain MRI and benefit from a L-dopa trial, all the more if there is no clear history of perinatal injury. This could be the "minimal" diagnosis workup in areas where NGS is not available for regular care. Ideally, a lumbar

TABLE 1 *Treatable causes of movement disorders that may mimic CP*

Disorder	Clinical Diagnostic Clues	Paraclinical Investigations	Treatment
GLUT1 deficiency	Paroxysmal episodes Worsening with fasting or exercise	Hypoglycorrhachia Normal brain MRI	Ketogenic diet Triheptanoin
Dopa-responsive dystonia	Diurnal fluctuations Oculogyric crises	Normal brain MRI	L-dopa
Dystonia/parkinsonism, hypermanganesemia, polycythemia, and chronic liver disease		Elevated blood manganese T_1-weighted hyperintensities of the globus pallidus, putamen, caudate, and dentate nuclei	Chelation therapy and iron supplementation
Ataxia with vitamin E deficiency	Head tremor	Low plasma vitamin E	High doses of vitamin E
Niemann-Pick disease type C	Supranuclear gaze palsy Enlarged liver or spleen	Positive filipin test Elevated serum levels of oxysterols	Miglustat
Biotin-thiamine–responsive basal ganglia disease	Episodes of subacute encephalopathy	T_2-weighted hyperintensities in the caudate nuclei and putamen	High doses of biotin and thiamine
Cerebrotendinous xanthomatosis	Chronic diarrhea Bilateral cataract	Elevated cholestanol T_2-weighted hyperintensities of the dentate nuclei	Chenodeoxycholic acid
Pyruvate dehydrogenase deficiency	Paroxysmal episodes	Elevated lactate T_2-weighted hyperintensities of the globus pallidus	High doses of thiamine

puncture would also be part of this minimal diagnosis workup not to miss an underlying diagnosis of GLUT1 deficiency, but its invasive nature automatically limits its usage. However, a simple blood test should soon be available, which should greatly facilitate screening for this treatable disorder.[23]

Author Roles

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A.M.: 1A, 1B, 1C, 3A, 3B

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