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VIEWPOINT

Making waves: The changing tide of cerebral palsy

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Cerebral palsy (CP) is a broad diagnosis unbound by aetiology and is based on a clinical examination demonstrating abnormalities of movement or posture. CP represents a static neurological condition, provided that neurodegenerative conditions, leukoencephalopathies and neuromuscular disorders are excluded. In paediatrics, the genetic conditions associated with CP are rapidly increasing, with primary and overlapping neurodevelopmental conditions perhaps better categorised by the predominant clinical feature such as CP, intellectual disability, autism spectrum disorder or epilepsy. Progress in molecular genetics may challenge what constitutes CP, but a genetic diagnosis does not negate the CP diagnosis. As clinicians working in the field, we discuss the changing tide of CP. Neuroimaging provides essential information through pattern recognition and demonstration of static brain changes. We present examples of children where a layered clinical diagnosis or dual aetiologies are appropriate. We also present examples of children with genetic causes of CP to highlight the challenges and limitations of neuroimaging to provide an aetiological diagnosis. In consultation with a geneticist, access to genomic testing (exome or genome sequencing) is now available in Australia under Medicare billing for children under the age of 10 with dysmorphic features, one or more major structural organ anomalies, (an evolving) intellectual disability or global developmental delay. We encourage the uptake of genomic testing in CP, because it can be difficult to tell whether a child has an environmental or genetic cause for CP. A specific genetic diagnosis may change patient management, reduce guilt and enable more distinctive research in the future to assist with understanding disease mechanisms.

Rocking the Boat

The borders of the definition of cerebral palsy (CP) are varied, and the landscape continues to change. In this paper, we describe some of the clinical challenges in navigating the borders of a CP diagnosis, but we also take the opportunity to report the positive impact molecular testing has had for our patients with CP. As clinicians and researchers in this field, we discuss the clinical utility of genomic testing in CP and strongly support the increased access to genetic testing for children with CP.[1]

CP occurs in 1.4/1000 live births.[2,3] CP is due to a permanent and non-progressive lesion affecting the developing brain, resulting in a disorder of movement and posture. CP is a diagnosis made on clinical examination. Aetiology does not form part of the definition of CP, making CP a heterogeneous and inclusive 'diagnosis' with varied comorbidities.[4] Omitting aetiology from the definition has precluded a certain degree of precision in clinical care and research to understand underlying disease mechanisms and causes, which is often not translatable to an individual level. The term CP is a descriptor for a constellation of clinical findings rather than a specific aetiological diagnosis. As such, children require further imaging and genetic investigations to determine the actual cause. It is, however, agreed that CP is not a neurodegenerative nor neuromuscular disorder, nor a leukoencephalopathy.[5]

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Navigating the Classifications

While a non-degenerative motor condition is central to CP, ongoing discussion surrounds how ataxia, dystonia and even hypotonia fit the CP definition.[6,7] Although the brain lesion in CP must be non-degenerative and CP is conceptualised and counselled to families as a non-progressive disorder, in reality, over time some complications of the disability do progress. This includes musculoskeletal problems, such as worsening contractures, joint damage and gradual deterioration of functional gait.[8] This is demonstrated further, for example, by the young child mobilising with a walker and functioning within Gross Motor Function Classification System (GMFCS) level III but, by the time they are 12, their mobility is not sustainably functional. A wheelchair rather than a walker becomes the primary mode of transport.[9] Yet, if this is not explained to parents, they may have unrealistic expectations or blame themselves for not accessing enough therapy. For those with more severe CP, functioning within GMFCS level V, some will have a decline in respiratory function and a premature death from respiratory disease.[10] Data from parent groups support the notion that transparent, honest and early counselling about these complications is essential.[11] Certainly, as we promote the effectiveness of early intervention, this should be balanced by explaining and counselling the progressive nature of some CP complications, removing parental guilt when they occur.

Stormy Seas

Some clinicians hold an outdated view that a diagnosis of CP mutually excludes other diagnoses. CP is associated with comorbidities in many children, including intellectual disability, vision and hearing impairment, communication difficulties, challenging behaviours, and epilepsy.[12] There is increasing recognition and open discussion of co-existing anxiety, autism spectrum disorder (ASD) and other psychiatric conditions.[13,14] There are multifactorial barriers to cognitive and psychiatric diagnoses. Access to specialist schools and aid funding in Australia is often based on physical disability, sometimes leaving the cognitive aspects untested. Additional barriers to identifying comorbidities include the presence of a physical disability and the use of a communication device during neurocognitive testing.

Neuroimaging at the Helm

The need for magnetic resonance imaging (MRI) for all children with CP is agreed upon, and a repeat scan should be considered if a cause has not been identified by 2 years of age.[15] However, neuroimaging alone does not always provide an accurate aetiological diagnosis, and a genetic diagnosis should be pursued. It is a combination of skill in correlating the constellation of neurological signs with the radiological phenotype, which requires an understanding of the timing and mechanisms underlying brain injury and developmental malformations. One scenario is children who fit the 'double hit' hypothesis: where an underlying genetic condition predisposes to injury visible on MRI. For example, Coffin–Siris syndrome is associated with a cortical malformation, yet there may also be co-occurring deep grey matter injury. Another example is a child with trisomy 21 with a cardiac defect who sustains a stroke in early life, yielding trisomy 21 plus CP. Therefore, children with any other syndrome, like trisomy 21, can still have definite white matter or grey matter injury on the MRI. However, if these children with dual diagnoses are included in a CP research cohort, they bring additional risks and complications of their genetic syndrome. With advances and access in genetic testing and increased awareness, dual diagnoses will become increasingly recognised. Another scenario is a child functioning within CP GMFCS level V, with agenesis of the corpus callosum which in isolation does not explain the severity of a physical disability. Or, an ex-23-week infant with a normal MRI brain scan but functioning within GMFCS level V should also prompt more thought regarding investigation for potential genetic causes unrelated to prematurity.

Charting a New Course with Genetic Aetiologies

It is estimated that up to one third of cases of CP are genetic.[16,17] Novel candidate genes for CP and non-canonical presentations of recognised genetic disorders are increasingly described.[16,18–21] This represents a major shift in our approach to, and understanding of, CP, especially over the past 5 years in the clinical and research settings, where causes of CP may be considered environmental, genetic or both.[22] (Fig. 1) Important environmental causes of CP include injury from prematurity which exposes the neonate to ischaemia, haemorrhage or both. Other injuries include deep grey matter injury, watershed injuries and stroke.[23] Injury can also be identified

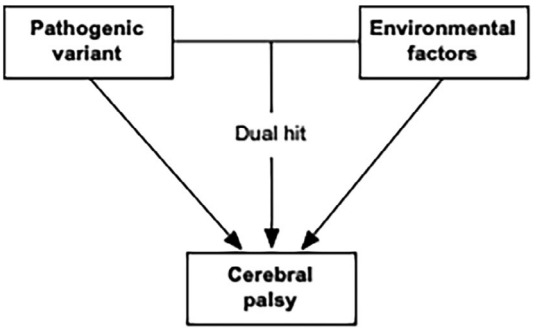

Fig. 1 Hypothesis of aetiologies cerebral palsy. This figure shows that cerebral palsy may be caused by a pathogenic variant, an environmental injury or both.

in term born children with uneventful neonatal courses. In CP due to injury, there is heterogeneity in timing, site and size of the brain injury, and overlapping injuries are common, which all broaden the phenotypic spectrum. A focus on 'causal pathways'[24] will likely yield more progress in the coming years as we understand the interplay between genetic and environmental factors.

To limit the diagnosis of CP to individuals with only an early acquired brain injury is also not straightforward. Injurious causes of CP are not just environmental and can be genetically mediated. Genetically mediated injury may appear like environmental injury, both clinically and radiologically. This has been shown for some with congenital hydrocephalus, whereby cases have been shown to have early brain development disturbed by a pathogenic variant mediating disruption, rather than secondary to the dynamic forces of cerebrospinal fluid accumulation.[21]

Another double-hit model of genetic and environmental causes resulting in CP, is seen in neonates with a *TEP1* mutation having microglial cells with increased vulnerability to injury in the presence of hypoxia.[25] Similarly, the *SPAST* or *ATL1* gene mutations traditionally associated with hereditary spastic paraplegia may have MRI changes in keeping with classic white matter injuries, including T2 subcortical scattered hyper-intensities and periventricular leukomalacia or other white matter abnormalities.[26] More recently, *CTNNB1* pathogenic variants are climbing the ranks as a relevant pathogenic variant in CP.[16] Mutations in the *COL4A1* and *COL4A2* genes can be inherited in an autosomal dominant pattern. These mutations show clinical variability, including intraventricular haemorrhage, porencephaly, polymicrogyria, schizencephaly or subependymal heterotopia.[27,28] Injury can sometimes be seen on antenatal scans. There may also be an associated spectrum of end-organ involvement, including cardiac, renal, ophthalmic and muscular complications.[27,29] Recurrent brain insults may occur, leading to progressive cerebral atrophy, even in the absence of clinical change.[30] A genomic diagnosis in certain conditions can alter management and improve clinical outcomes in up to 50% of cases.[31,32]

But Beware the Rocks

Red flags for a genetic diagnosis include atypical features such as neonatal seizures beyond 12 hours of age, a motor phenotype of hypotonia, profound intellectual disability or ataxia.

Table 1 Examples of likely genetic causes of cerebral palsy

Patient number	Gestation / Neonatal history	Clinical features	Childhood seizures	Neuroimages of patients 1-6, as shown in Figure 2	Pathogenic variant / Syndrome diagnosis	Diagnostic outcome
1	Term, singleton Neonatal seizures	Profound hypotonia Dysmorphic Pituitary dysfunction	Mycolonic Tonic–clonic Atypical absence Gelastic	Volume loss with prominence of extra-axial spaces, especially the frontal and temporal lobes. T2 hyperintensity within the periventricular white matter bilaterally. Non-myelination of the white matter within the temporal lobes bilaterally	*PURA* syndrome	Genetic cause of cerebral palsy
2	Premature, multiple	Athetosis	Prolonged generalised tonic seizures	MRI – initially normal.	*GNA01* mutation	Not cerebral palsy – Initial MRI initially normal and this condition is often slowly progressive
	Neonatal seizures – day 3 of life			Second MRI – atrophic and non-myelination of the anterior 2/3 of the left temporal lobe with involvement also of the of the left hippocampus. Mild lateral ventriculomegaly, more pronounced on the left than the right		Management with Deep Brain Stimulation is effective treatment
3	Premature, multiple	High forehead hypertelorism	None	Corpus callosum dysgenesis, dysplastic lateral ventricles and generalised reduced white matter volume. Dysplastic brainstem	*CLTC* mutation	Genetic cause of cerebral palsy
4	Term, singleton	Microcephaly	Myoclonic	Loss of periventricular white matter ex-vacuo dilatation of the lateral ventricles, high signal in periventricular white matter with involvement of the deep white matter and the thalami. Relative sparing of the peripheral white matter	Awaiting trio genomic sequencing	Possibly not cerebral palsy – progressive changes with new thalamic injury despite no surgical or medical history
5	Term, singleton	Tall stature	Tonic, atonic	>30 T2/FLAIR hyperintensities in the subcortical white matter, predominantly in the frontal lobes. Moderate third and lateral ventriculomegaly, with mild right frontal periventricular cystic change	Trio genomic sequencing – no genetic cause identified	Likely genetic cause of cerebral palsy with history of epilepsy
6	Term, singleton	Hypotonia ataxia	Focal Epileptic spasms	Mildly prominent spaces around cerebellar folia in keeping with cerebellar atrophy	*STXBP* mutation	Genetic cause of cerebral palsy with prominent history of epilepsy

Unsurprisingly, the yield is also higher for those with dysmorphic features, family history or term born infants.[33,34] Congenital anomalies are recognised at an increased prevalence in children with CP.[35] A predominant dystonic phenotype, with a normal MRI and response to dopamine, also increases the chance of a genetic aetiology.[36] The diagnostic yield for pathogenic variants is higher in children with a malformation, normal imaging or miscellaneous patterns of injury such as delayed myelination, cerebral atrophy or ventriculomegaly (in the absence of identified ischaemic or haemorrhagic change).[23]

Predicting a genetic cause of CP is not always possible based on the clinical or radiological phenotype. A recent small study showed that the genetic diagnosis rate of children with and without risk factors for CP – such as extreme prematurity, an intraventricular haemorrhage or birth asphyxia – showed no difference in the rate of pathogenic variants identified.[37] This

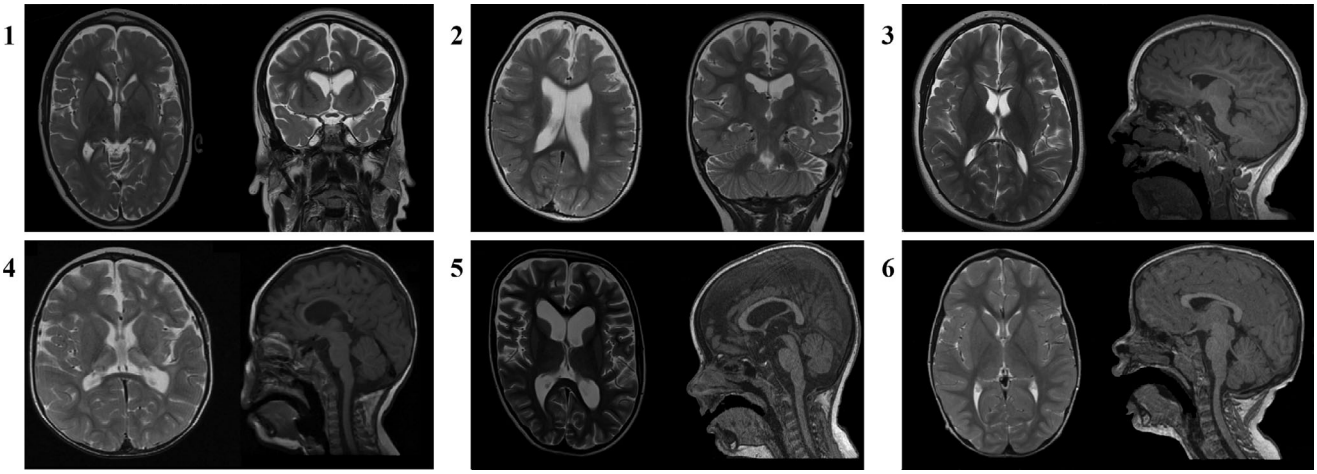

Fig. 2 Neuroimages associated with examples of likely genetic causes of cerebral palsy. Neuroimages of patient number 1–6 which correspond to Table 1.

highlights that the yield for identifying children with a genetic cause of CP without risk factors for CP is still high enough to add value.[25,37] The yield may be lower in some children with extreme prematurity or an intraventricular haemorrhage. However, an existing white matter injury or grey matter injury does not negate the pursuit of a genetic diagnosis, nor should it discriminate in the access of a genetic diagnosis. Clinicians have a responsibility to search for an aetiology.

Learning the Ropes

So, what taxonomy should we use in CP? Classically, a neurologist would not accept a complication of a disorder without first trying to find the primary diagnosis or understand the aetiology. The epilepsy literature, which is 20 years ahead, provides structure and learnings for thinking about CP. The first tier diagnostically is the aetiology of epilepsy. Epilepsy gene panels provide aetiological diagnoses.[38] Epilepsy pathogenic variants may be *de novo*, show somatic mosaicism (e.g. a mildly affected parent with a more severely affected child), or be recessive.[38] There may be vast genotypic and phenotypic heterogeneity.[38] This means that the child will need clinical monitoring to assess their cognitive function and physical disability as this is not explained entirely by the pathogenic variant.

Notably, several genes can cause one epilepsy syndrome and, conversely, one gene might be associated with phenotypic variation. Pathogenic changes, once thought to be seen only with neurodegenerative conditions, are also found in static conditions, meaning that the clinical diagnosis and clinical monitoring, together with the genetic diagnosis, are equally important. The clinical findings and descriptive details will help differentiate between a static condition and a degenerative/encephalopathic condition. Just like in CP, a clear history (and examination) is enough to make a diagnosis of epilepsy, but further investigation is required to understand the underlying aetiology.

Facing the Crosswinds of Challenging Examples

With advancing therapy, some previously degenerative conditions may be halted. Children with metabolic conditions, such as phenylketonuria, have historically been excluded from a diagnosis of CP, mainly due to the progressive nature of metabolic disorders in the absence of effective treatment. For many, dietary, enzyme or other therapies have altered the trajectory, making their condition static. Do they now have a 'static condition' and, therefore, can we consider them to have CP?

At a subtle level, there are clinical differences when the primary phenotype is an intellectual disability/ASD rather than a physical disability, even when there is an associated physical disability. For example, a child with a *TAF1* mutation, an x-linked recessive cause of intellectual disability, may be non-verbal, develop an unsafe swallow requiring gastrostomy feeding, have a movement disorder but be crawling and taking supported steps yet still need to progress to bilateral varus derotation osteotomies. Perhaps, many named genetic syndromes fit broadly under this category. Some clinicians offer the term Severe Neurological Impairment,[39] which describes children with more significant impairments, allows for progressive symptoms and avoids the historical ambiguity of CP.

Light on the Horizon

In Australia, as of May 2020, Medicare-funded trio whole-exome sequencing or whole-genome sequencing is available for testing of patients and their biological parents, in children under the age of 10 with dysmorphic features, one or more major structural anomalies or (an evolving) intellectual disability or global developmental delay, in consultation with a geneticist. Access to this test could be through phone advice or via a formal referral and review by a geneticist. Re-analysis is essential for those initially thought not to have a known pathogenic variant identified. A microarray should be undertaken first as abnormalities are

detected between 7 and 15% of cases.[40] A neurometabolic work-up is still required for special cases; for example, sick acidotic neonates, consanguinity or family history of unexplained infant death. Access to genetic testing in Australia is not a rate-limiting step the way it may be in other countries. Using this technology, we present some current diagnosed and undiagnosed examples. (Table 1, Fig. 2).

Full Steam Ahead!

The term CP carries important meaning for clinicians, families and funding bodies, as individuals with CP share management similarities. However, when using a diagnosis of CP, it is imperative to determine underlying aetiology. In children presenting with suspected CP, the approach to diagnosis should include a clinical examination to determine the CP subtype and identify comorbidities to characterise the predominant phenotype: physical disability, intellectual disability, ASD, or epilepsy. MRI is essential to determine the presence and types of brain abnormalities, in conjunction with genomic testing. Genomics is transforming practice in CP, just as it has for many conditions and the landscape of genetic disorders which cause CP is rapidly evolving. Watch this space. Get on board with testing your patients.

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My Dad by Gabby Cooper (age 15) from Operation Art