June 2016

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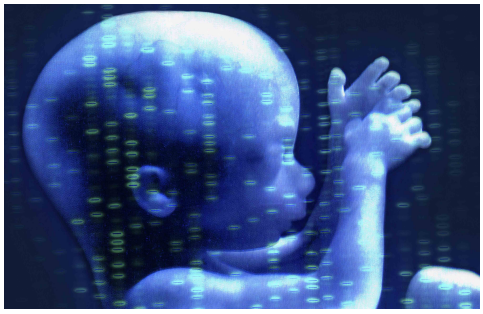
A Cause for Cerebral Palsy: Could It Be in Our Genes?

New technologies are allowing researchers gain new insights, with the near-future implications for prevention, therapy and interventions.



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Every case of cerebral palsy is unique and never the same disease twice. This is a challenge for families, clinicians, and investigators alike. Its onset, the neuromotor impairment pattern, severity across functional domains, the presence of multiple health conditions or diseases, secondary complications and available interventions make it nearly impossible to categorize in one way. This type diversity, not surprisingly, also applies to the multiple causes for cerebral palsy.

A wide range of causes and risk factors have been identified that may arise prenatally (prior to labour and delivery), perinatally (during the birthing process) or postnatally (after birth in the first year of life). Traditionally, given the evaluative tools available to clinicians and investigators, the emphasis for research has been on acquired causes for cerebral palsy. This includes birth asphyxia, trauma, infections, stroke or malformations of the brain itself.

This knowledge informs prevention strategies, leading to disappointing results. For example, in the past half century, electronic monitoring efforts during labour and delivery have been directed at detecting a baby at risk for asphyxia to accelerate delivery through surgery. This resulted in six times more caesarean sections for term babies, with no important decrease in the frequency of cerebral palsy.

A child with cerebral palsy and a normal MRI scan (up to 15% of cases) further

indicates that asphyxia is not a cause, but perhaps a risk factor. Equally mystifying are children who never develop cerebral palsy with a similar risk exposure (eg lack of oxygen, prematurity) to children who do develop cerebral palsy. A number of observations over the years have suggested that genes may play a role in both causing cerebral palsy and modifying the risk for developing cerebral palsy in a child with exposure to a known risk factor.

Documented familial occurrences of cerebral palsy, an increased risk of co-occurring cerebral palsy in identical twins, a higher frequency of consanguineous (iebiologically related) parental matings, the identification of concurrent congenital anomalies or intrauterine growth restriction (ie a fetal weight that is below the 10th percentile for gestational age), and rare cases of cerebral palsy attributable to a known defect in a single gene, are each an observation suggesting a potential genetic role. Taken collectively, these observations come together to make a strong case for asupposed genetic role.

Until recently, investigators have focused their search for genetic causes on small restricted subsets of children with cerebral palsy. Similarly, investigators have been hampered until recently by technologies available, and their resolving power, to identify abnormal genes. Several advances have enabled investigators to address and surmount these barriers in the search for genetic causes.

Regional and national registries of cerebral palsy have been established in both Australia and Canada. Systematically, and with minimal bias, these registries identify a large number of cases of cerebral palsy that captures the diversity of this complex disease.

Genetic technologies have emerged that can detect important changes at a high resolution. Specifically, it detects changes in the number of copies of segments of DNA (high resolution microarray or actually sequence coded genes across the genome, looking for important mistakes in coding (whole exome sequencing).

These techniques allow investigators to cast a wide net in the hunt for genetic causes without a priori restricting themselves to looking at one or a few suspected genes (nb: there are 25,000 genes of which half code for a protein that can be located in the brain). The key enablers were linking these two advances and the willingness of families to have biological samples (saliva or plasma) drawn from their children (and sometimes from parents themselves) for genetic analysis.

The results from these efforts have been published recently and are indeed shifting the fundamental approach for research. In unselected cases, in anywhere between 15-30% of cases of cerebral palsy a genetic abnormality can be identified. Furthermore, there does not appear to be a consistent set of clinical clues to suggest that a genetic cause may be identified. Also, a large variety of genetic abnormalities can be identified with no single one predominating. Finally, genetic abnormalities can be identified in those cases that had been thought to be causally explained by an already known acquired cause.

These findings have an immediate impact on how clinicians should evaluate cerebral palsy. At present, practice guidelines suggest that only in certain rare cases should genetic causes be searched for. CGH is presently available as a laboratory test to clinicians and should now be considered as a first-line test, like neuroimaging, in the evaluation of the child with cerebral palsy. It can be anticipated that this will be supplanted in the intermediate term (next five years) by whole exome sequencing then by whole genome sequencing. Finding genetic factors at play also will have obvious implications in family counselling and planning.

The genetic findings explained thus far in cerebral palsy also have near-future implications for prevention, therapeutic and intervention efforts. New causal pathways are now being identified that may be open to alteration to either prevent the development of cerebral palsy or enhance the resilience or recovery of children exposed to a known risk factor.

Prenatally identified genetic factors may play a 'susceptibility' role that enhances or minimizes the 'hit' of an environmental agent (eg asphyxia or prematurity). This may then assist in identifying subsets of infants at high risk who would most likely either benefit from intensive preventative efforts or intervention efforts to promote recovery.

The net result of these genetic findings is a substantial enhancement in our understanding of the mechanisms that interact to result in cerebral palsy, the most common physical disability encountered in childhood.

From this heightened understanding, one can reasonably anticipate improved and informed care that is empowering for families and that provides the hope for better outcomes for children; both those born with cerebral palsy and those yet to be born but at risk.

Take home points for clinicians

- Cerebral palsy is a complex and widely diverse disorder
- Recent studies using a variety of methodologies have identified genetic abnormalities in 15-30% of unselected cases of cerebral palsy culled from populationbased registries
- Comparative genomic hybridization (CGH) or high resolution microarray is now widely available to clinicians and should be considered as a firstline test, along with neuroimaging, in the diagnostic evaluation of cerebral with

clinically documented or suspected cerebral palsy
- It can be expected that with time, the preferred genetic testing will shift to whole exome sequencing and then whole genome sequencing. This shift will depend on local costs, availability and interpretative capabilities

Take home points for families

- Cerebral palsy is a complex and widely diverse disorder
- A large variety of causes and risk factors may interact to cause a particular child's cerebral palsy
- There is evidence in a large subset of children with cerebral palsy that abnormalities in the genetic code can be identified
- These genetic abnormalities may contribute to the cause of a child's cerebral palsy or that child's response to an acquired risk factor for cerebral palsy
- Testing for these abnormalities is now clinically possible
- A genetic cause does not imply any fault on the part of either parent.

Want to learn more on the topic? Suggested articles:

"Cerebral Palsy: Causes, pathways and the role of genetic variables". MacLennan AH et al. American Journal of Obstetrics & Gynecology 2015, Vol. 213, Issue 6, Pages 779-788

"Clinically relevant copy number variations detected in cerebral palsy". Oskoui M et al. Nature Communications 2015, Vol. 6, Article number 7949