EUROPEAN ACADEMIC RESEARCH
Vol. IV, Issue 9/ December 2016

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

Genetic Insight into Cerebral Palsy

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Abstract:

Cerebral palsy (CP) is heterogeneous with different clinical types, co- morbidities, and brain imaging patterns, causes, and now also heterogeneous underlying genetic variants. Few are solely due to severe hypoxia or ischemia at birth. Epidemiological studies have shown that the origins of most Cerebral Palsy are prior to labour. Increased risk is associated with preterm delivery, congenital malformations, intrauterine infection, foetal growth restriction, multiple pregnancy, and placental abnormalities. Hypoxia at birth may be primary or secondary to pre-existing pathology. Until recently; 1-2% of Cerebral Palsy (mostly familial) had been linked to causative mutations. Recent genetic studies of sporadic Cerebral Palsy cases using new-generation sequencing show that 14% of cases have likely causative single-gene mutations and up to 31% have clinically relevant copy number variations. The genetic variants are heterogeneous and require function investigations to prove causation. Whole genome sequencing, fine scale copy number variant investigations, and gene expression studies may extend the percentage of cases with a genetic pathway. Clinical risk factors could act as triggers for Cerebral Palsy

where there is genetic susceptibility. These new findings should refocus research about the causes of these complex and varied neurodevelopment disorders.

Key words: causes, cerebral palsy, DNA variants, epidemiological risk factors, genetic variants, genomics, heterogeneity, whole genome sequencing

INTRODUCTION

Cerebral palsy is the result of a combination of events either before, during or after birth that can lead to an injury in a baby's developing brain. Cerebral palsy is a common disorder of childhood with an incidence of 1/250 – 1/1,000 births (Pharoah et al 1987; Bundy and Alam 1993) Inherited factors are thought to contribute to approximately 2% of cases in European populations (Hughes and newton, 1992; Mitchell and Bundey .1997) however, with increased understanding of genetic pattern that cause neonatal brain disorder, it is clear that de novo mutations and recessive disorders can often simulate"no genetic" conditions. The first description of cerebral palsy as a clinical entity is attributed to William John Little, an eminent British orthopaedic surgeon. In 1861, he wrote a monograph in which he proposed for the first time an association between perinatal asphyxia and poor neurological out comes later in life. (Little WJ 1861). Genetic form of the disease accounts for 2% of cases in most countries but contribute a larger population in populations with extensive inbreeding (Hale Mc DP et al 2000).While cerebral palsy is not a hereditary condition, researchers have discovered that hereditary factors can predispose an individual to cerebral palsy. Although a specific genetic disorder does not directly cause cerebral palsy, genetic influence can cause small effects on any genes. Genetic influence can also develop gene to gene interactions with multiple environmental influences. This interaction is called

"complex inheritance" or "multi factorial inheritance" and may explain why cerebral palsy can have a genetic cause. Some genetic contribution to obstetric risk factors includes preterm birth, placental abruption, foetal growth restriction, chorioamnionitis, preeclampsia and breech presentation. Two new born exposed to the same environmental stressors will often have very different outcomes," this suggests that our genes impart resilience or conversely a susceptibility to injury (Oskoui etal 2015).

Cerebral Palsy is divided into four main categories: spastic, athetoid, ataxic, and mixed forms, according to the type of movement disturbance [Hughes and Newton, 1992; NINDS, 2005]. Spastic Cerebral Palsy accounts for approximately70–80% of cases, and is subdivided into hemiplegic, diplegic, quadriplegic, and monoplegic types, depending on which limbs are affected. Spastic Cerebral Palsy patients show increased deep tendon reflexes, hypertonic, and weakness. Scissors gait is common. The most severe form of spastic Cerebral Palsy, spastic quadriplegia is frequently accompanied by dysarthria .Ataxic cerebral palsy accounts for 5 to 10% of all forms of cerebral palsy and it is estimated that approximately 50% of ataxic cerebral palsy is inherited as an autosomal recessive trait (Hale Mc DP et al 2000). Athetoid cerebral palsy accounts for 5 to 10% of all cerebral palsy (Hagberg B et al 1994, Stanley F et al 2000.) and is characterized by dysfunction of the basal ganglia leading to impairment of the postural reflexes, arrhythmic involuntary movements, and dysarthria, with sparing of sensation, ocular movements, and often intelligence (Foley J et al 1983). Ataxic cerebral palsy occurring without any predisposing events is likely to be genetic in approximately half the cases and the same is true for idiopathic athetoid cerebral palsy (Hughes and newton 1992).spastic cerebral palsy is the most common sub type and has a low over all recurrence risk. Spastic cerebral palsy that is both symmetrical and idiopathic accounts for <4% of all cerebral palsy cases, but its recurrence risk in sibs is 1/8(Bundey and griffths 1977) most cases are

autosomal recessive, but rare autosomal dominant and X linked forms have also been described (Bundey and griffths 1977; Bundy et al 1978).There are no previous reports of genetic linkage for autosomal recessive "true" spastic cerebral palsy. According to WHO estimation, 10% of the global population has some form of disability due to different cause: in India it is 3.8% of the population. Nearly 15—20% of the total physical handicapped children suffer from cerebral palsy. For India the estimation incidence is around 3/1000 live birth show ever being a developing country, the expected actual figure may be much higher. Despite the advancement in modern technology and improved neonatal care, stagnant or increasing incidence of cerebral palsy has been observed (Apexa.G et al 2011) disability It is among the 60% of cases that the rarer genetic forms of cerebral palsy occurs approximately 2% of all cases of cerebral palsy in Swedish and English children are due to a genetic causes(Gustavson et al 1969,Bundy and Griffiths 1997)most of this cases have no recognized adverse pre or post partum events and have marked symmetry of the neurological signs. Thus it follows that hemiplegic and monoplegic are rarely if ever genetic. The purpose of this study was to analyze the role of genetic factors in cerebral palsy. This was achieved by reviewing the literature for genetic causes of cerebral palsy .An understanding of genetic factors is vital to our understanding of the casual pathways in cerebral palsy and for accurate counselling of parents regarding the risk of recurrence.

Review

In the study, done by **Scherer et al 2015** which was published in Nature Communications, genetic testing was performed on 115 children with Cerebral Palsy and their parents, with environmental risk factors previously identified for many of the children. Surprisingly, ten percent of the children studied had a group of clinically relevant genetic changes, called copy number variations (CNV). Some were inherited from their parents, while others were new mutations. These genetic changes are found in less than one percent of the

general population. In five percent of the children with CNVs the genetic changes were small but they affected multiple genes. 'It's a lot like autism, in that many different CNVs affecting different genes are involved, which could possibly explain why the clinical presentations of both these conditions are so diverse. In the remaining five percent of children with CNVs the genetic changes were considerably larger. 'For five percent, these big changes are the cause of their Cerebral Palsy. The authors are now urging the medical community to consider routinely genetic testing for the diagnostic assessment of children with the condition.

Oskoui et al (2015) could explain diverse clinical presentation of disorders. They used data from Canadian cerebral palsy registry; these researchers conducted genetic testing on 115 children with cerebral palsy and their parents, many of whom had other recognized cerebral palsy risk factors. The researcher discovered that around 10% of the children had copy number variations (CNVs) affecting genes considered clinically relevant to the disorder. CNVs are structural changes to the DNA of a genome involving gains or losses of genetic material that can lead to disease. The researchers also found that these are several different genes involved in the development of cerebral palsy, which could explain why children can be affected by the disorder in a diverse range of ways.

D.P McHale (1999) has clinically characterized consanguineous families with multiple children affected by symmetrical spastic cerebral palsy, to locate recessive genes responsible for this condition. The eight families studied were identified from database of patients in different regions of the United Kingdom. After ascertainment and clinical assessment, they performed a genome wide search for linkage, using 290 polymorphic DNA markers. In three families a region of homozygosity at the chromosome 2q24-q25 was identified between the markers D2S124 and D2s148 the largest family gave a maximum LOD score of 3.0 by multipoint analysis

(HOMOZ) the maximum combined multipoint LOD score for the three families was 5.75 and the minimum region of homozygosity is -5 cM between the marker D2S124 and D2S2284 they have shown that a proportion of autosomal recessive symmetrical spastic cerebral palsy maps to chromosome 2q24-25.

Anna Rajab (2006) reported on a detailed clinical description of a large consanguineous family from Oman showing spastic Cerebral Palsy with microcephaly and mental retardation. Our analysis provides evidence that a heritable factor causes these symptoms in this family, and reiterates the importance of recessive genes as a cause of Cerebral Palsy. (almost exclusively from northern Pakistan) and non Asian populations in Yorkshire, united kingdom has reported a two fold increase in cerebral palsy prevalence in the Asian population(3.18 cases per 1000)(Sinha et al .,1997)since about 60% of the Asian families in this study had a known history of consanguineous marriages, and since about a third of the affected children in these families had a first or second degree relative with the same type of Cerebral palsy, recessive genes may have caused the increased incidence. An independent study from Saudi Arabia reported a 2.5 fold increase in the occurrence of cerebral palsy in consanguineous families (Al-Rajesh et al 1991), also strongly suggesting that the recessive forms of cerebral palsy exist.

Mitchell and Bundey (1997) used homozygosity mapping ti identify genetic loci involved in spastic cerebral palsy in right consanguineous families originating from the mirpur region of Pakistan. The affected children have a symmetrical, non progressive spasticity and no adverse perinatal history or obvious underlying alternative diagnosis

David J et al (2001) studied 20 cases of athetoid cerebral palsy and identified three families in whom recurrence could be confirmed. Combining data from the present study with previous studies (Foley J et al 1983, Fletcher NA et al 1996, Gustavson KH et al 1969,Palmer L et al 1994,Christensen E et

al 1967)suggests a frequency or recurrence of athetoid cerebral palsy within families of 1.6%(95% cl 0.6 – 2.6%). A final clue to the existence of a genetic aetiology in cerebral palsy is the presence of congenital abnormalities outside the central nervous system, suggesting an antenatal rather than a perinatal cause (Gibson et al 2006). Children with cerebral palsy have been observed to have an increased incidence of both major (Palmer L et al 1994, Nelson KB 1986) and minor(Coorsen EA et al 1991) malformations compared with the general population. Although a small increase in the incidence of minor malformations in children with athetoid cerebral palsy was observed in one study,(Foley J et al 1983)we did not observe an increase in either major or minor malformations in our population. Although most cases of athetoid cerebral palsy are currently attributed to perinatal complications. It has been suggested that genetic factors also play a significant role. There are several possible explanations for this observation. First, genetic factors and birth asphyxia may not be mutually exclusive in some cases; both genetic factors and birth asphyxia might be necessary but not individually sufficient to cause athetoid cerebral palsy. Alternatively, an underlying genetic factor might directly or indirectly lead to both an increased risk of birth asphyxia and to athetoid cerebral palsy .Secondly; the role of either birth asphyxia or genetic factors may have been over emphasized by previous authors. The former because of the difficulty in defining birth asphyxia clinically and the latter because of a reporting bias in favour of familial cases

Shevel et al (2015) said that Genetic causes have long been suspected because of the link with congenital malformations, and increased risk in consanguineous families and monozygotic twins.(Schaefer 2008) Although initially candidate gene association studies suggested that several genes may be linked to Cerebral Palsy, the power of these studies was low and multiple comparisons weakened their validity.(Gibson et al 2005 , Gibson et al 2006) A multivariable analysis of

39 candidate genes from single-nucleotide polymorphism association studies with Cerebral Palsy was conducted with statistical allowance for type I error. This study did not statistically confirm previous gene associations in Cerebral Palsy causation (Callaghan et al 2012)A recent study showing an association with the apolipoprotein E e3 allele speculated that those with the APOEe2 and APOEe4 alleles were more likely to die in utero (Stoknes et al 2015)

Rajab et al (2006) has done new-generation DNA sequencing and told that the focus of genetic investigations in Cerebral Palsy shifted from gene association studies to the identification of the likely causal variants. Several of the currently known single-gene causes of Cerebral Palsy have been identified through study of families with ≥2 individuals with Cerebral Palsy, such as the *KANK1*, *AP4MI*, and *GAD1* gene mutation .(Lerer et al 2005,Verkerk et al 2009,Lynex et al 2004,Hemminki et al 2007)Until recently, though, only a few singleton cases with Cerebral Palsy had been resolved. Cases with autosomal recessive, rare autosomal dominant, or X-linked forms have also been described.(Mc Hale et al 2013).One example of a success of an identification of a novel gene and mutation leading to Cerebral Palsy is the *ZC4H2* gene. With the aid of whole exome sequencing (WES) or X-chromosome exome sequencing across a large set of families with different clinical presentations, primarily intellectual disability, mutations have been identified in the zinc-finger gene ZC4H2 in 5 different families and at least 3 singletons. Interestingly, the clinical presentations of ZC4H2 gene mutations are broad and variable within and between families, including Cerebral Palsy spasticity phenotype and shared comorbidities, namely intellectual disability and seizures.(Hirata et al 2013) Functional studies of these variants using zebrafish model showed that loss of the ZC4H2 protein function caused abnormal swimming and impaired alpha-motoneuron development. In mouse hippocampal neurons, transiently expressed ZC4H2 protein localized to the postsynaptic

compartment of excitatory synapses and loss of ZC4H2 function led to reduced dendritic spine density and impaired central and peripheral synaptic plasticity (Hirata et al 2013) Such follow-up functional studies are essential to confirm Cerebral Palsy pathogenicity and better understand molecular pathways involved and provide explanation for complex and variable clinical presentations.WES is indeed a powerful tool to identify efficiently the likely causative genetic variant. In particular, sequencing of multiple family members can reduce the number of candidate DNA variants to 1 or 2 and thus also lead to timely and precise diagnosis. This was nicely demonstrated in a family initially diagnosed with a Cerebral Palsy-like movement disorder, where 3 members with "hereditary benign chorea" were identified to carry a 7-base pair deletion in exon 1 of the *NKX2-1* gene. The mutation is predicted to lead to a frame shift in protein translation and subsequent premature termination of *NKX2-1* messenger RNA translation and NKX2-1 functional haploinsufficiency.(McMichael et al 2013)Recent investigations of genetic causes in a large cohort of singleton Cerebral Palsy cases using WES shows that the proportion of the cases carrying plausible genetic mutation is much larger than previously thought. At least 14% of nearly 200 singleton cases with Cerebral Palsy studied have been found to have a plausible genetic mutation, de novo or inherited (McMichal et al 2015)A further 44% had candidate variants that are yet to be resolved in regard to their causation of the Cerebral Palsy. The percentage of cases with a genetic mutation is likely to rise as larger cohorts are studied, new Cerebral Palsy genes are discovered, and whole genome sequencing is routinely performed. It is likely that at least a proportion of the Cerebral Palsy cases will be explained by more complex genetics and not just single major gene effect. Our WES study identified likely causative genetic contributions to Cerebral Palsy. Variants that may predispose to Cerebral Palsy by interacting with environmental triggers have yet to be identified. Predisposing variants would likely be oligogenic or polygenic and thus

additive in nature and would require genomewide association studies and gene-environment investigations on a large sample of Cerebral Palsy cases and controls. Such variants would increase the risk of a Cerebral Palsy phenotype and not be deterministic of Cerebral Palsy. Established environmental risk factors for Cerebral Palsy, such as IUGR, infection, and prematurity, may interact with predisposing genetic variants and potentiate and multiply the chance of a Cerebral Palsy outcome.

CONCLUSION

Discovering the cause of a child's disability is an important step to be taken in managing it. Parents want to know why their child has particular challenges. Finding a precise reason opens up multiple vistas related to understanding, specific treatment, prevention and rehabilitation. This study will provide the impetus to make genetic testing a standard part of the comprehensive assessment of the child with cerebral palsy. In the near future, it will be possible to test for many of the putative or validated genes that have been associated with Cerebral Palsy to date. This panel of different pathogenic genetic variations contributing to the Cerebral Palsy spectrum is very likely to grow over the next decade, and should open a new direction into the causes of Cerebral Palsy and challenge previous medico legal assumptions about the culpability of the accoucheur.

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