



Analysis of Genetic Factors in Children with Cerebral Palsy

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ABSTRACT

Cerebral palsy is a group of permanent limb posture and movement abnormalities caused by certain injuries to fetal or neonatal brain before its growth and development is completed. It is reported abroad that the incidence of cerebral palsy in live births (including full-term and preterm infants) is about 1/500, which is the most common disability disease in children. Despite many epidemiological studies, the cause of the epidemic has not yet been identified, because cerebral palsy is a complex group of symptoms, rather than a simple disease which is usually diagnosed clinically around the age of one. Some severe complications during pregnancy, such as placental abruption, umbilical cord prolapse, and uterine rupture, significantly increase the risk of cerebral palsy, but in general these factors account for only a small proportion of cerebral palsy. At present, the major risk factors for cerebral palsy widely known at home and abroad are preterm infants, intrauterine infections or maternal fever at birth, ischemic stroke, congenital malformations, fetal intrauterine abnormal growth, and multiple pregnancies. In addition, a great deal of evidence suggests that although genetic factors are not the primary cause of cerebral palsy, they may increase genetic susceptibility to cerebral palsy. Any kind of pathogenic factor reaching a certain degree of severity may cause cerebral palsy. But more often than not, multiple risk factors jointly destroy the body's defense mechanism and eventually lead to cerebral palsy.

Key Words: Hereditary Diseases, Hereditary Thrombophilia, Preterm Infants, Cerebral Dysplasia, Congenital Metabolic Disorder.

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Introduction

In recent years, studies have suggested that genetic factors play an increasingly important role in cerebral palsy. For example, those who have close relatives with epilepsy, cerebral palsy or mental retardation account for 60% of cerebral palsy patients. The following is chromosome abnormality, which is often manifested as deformity, accompanied by abnormal myotonia and ataxia, which constitutes a number of syndromes (Feng *et al.*, 2001). Cerebral palsy in children may have a variety of identifiable genetic

factors, including significant cognitive deficits (mental retardation), specific facial features, and apparent congenital anomalies (Hu, 2003). Other genetic diseases associated with cerebral palsy are mostly caused by genetic mutations, such as Huntington's disease, demyelinating disease, Friedreich ataxia, Rett syndrome, Angelman syndrome (abnormality of chromosome 15 and UBE3A mutation), hereditary spastic paraplegia, LICAM-related abnormalities, ARX mutation/West syndrome, etc (Bodensteiner and Johnsen, 2005).

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At present, genetic linkage studies have begun to identify the “decisive genes of cerebral palsy” through population studies, such as the presence of a genetic site associated with ataxia cerebral palsy on chromosome 9 p12-29q and the presence of an autosomal recessive genetic site of spastic cerebral palsy on chromosome 2 q24-25, which is expected to provide clues for further investigation of genetic causes of cerebral palsy.

Hereditary Thrombophilia (Tethered Disease)

At present, a large number of studies on the relationship between hereditary thrombophilia and adverse pregnancy outcomes all involve cerebral palsy (Li *et al.*, 2001). Ischemic perinatal strokes (IPS) is a disease resulting in significant neurological sequelae in perinatal infants, which occurs from 28 weeks after pregnancy until 28 days after birth, with incidence rate of 1/2000-1/3000 live births. Image findings suggest that IPS commonly occurs in the left middle cerebral artery of the fetus, so congenital hemiplegia caused by IPS is more likely to involve the right limb, and other long-term sequelae include spastic diseases and language development disorders. About 30% of full-term or near full-term children with hemiplegic cerebral palsy are due to IPS, so IPS is considered to be the leading cause of cerebral palsy in full-term and near full-term perinatal children. IPS is commonly seen in both boys and non-Hispanic blacks, and the reasons for this racial difference are unclear. Potential risk factors for IPS mothers have been found to include history of thrombotic disease, infertility, pre-eclampsia, premature rupture of the membranes >24 hours, chorioamnionitis, maternal autoimmune diseases and the formation of autoantibodies (platelet allograft I), and anti-phospholipid syndrome. Potential risk factors in the fetus or newborn include: collagen IVa1 mutation, hereditary thrombophilia, twin transfusion syndrome, fetal or neonatal polycythemia, and congenital heart disease, neonatal hypoglycemia in preterm infants, persistent fetal circulation, fetal growth restriction, fetal or neonatal infections, and meningitis. The autosomal dominant inheritance of cerebral palsy associated with these coagulation disorders has been identified and is mostly caused by major thrombotic events and can be traced back to a distinct family history of thrombotic disease (Raiu *et al.*, 2007).

If such a family history is confirmed, further detailed examination of the patient for

ischemic stroke should be considered. In contrast, what is more common is the so-called “mild” hereditary thrombophilia, such as the Leiden mutation of coagulation factor V G1691A, prothrombin II G20210A mutation, methylene reductase gene mutation and hyperhomocysteinemia, with an incidence rate accounting for between 7% and 30% of the total population (Lin *et al.*, 2001). These diseases are usually associated with adverse pregnancy outcomes, which usually lack or are even completely free of family history.

The relationship between these mild thrombophilia and adverse pregnancy outcomes and/or cerebral palsy is summarized as follows:

(1) It has been confirmed that porencephalen and hemiplegic cerebral palsy are associated with Leiden mutation of factor v;

(2) If there are any clinical or imaging indications of prenatal or perinatal stroke, infantile cerebral palsy is strongly associated with thrombotic factors;

(3) The risk of cerebral palsy is further increased by various factors such as pre-eclampsia, premature rupture of membranes, fetal or neonatal infection;

(4) Even if there is no imaging evidence of perinatal stroke or vascular accident, juvenile thrombophilia can be an independent risk factor for cerebral palsy.

Preterm Infants

In general, cerebral palsy is most common in preterm infants, with a reported total incidence rate of 86/1000 in preterm infants with very young gestational age (≤ 32 weeks), compared to the incidence rate of 1/1000 in full-term infants. Recent studies have shown that preterm infants have some specific genetic markers, linkage, or genetic polymorphisms, and some evidence suggests that genetic susceptibility is associated with spontaneous preterm birth and premature delivery. First, personal history or family history is the primary risk factor for spontaneous preterm birth and premature delivery. At the same time, the risk of premature childbirth also has racial susceptibility. Even if the influence of social class and economic level is controlled, the premature childbirth rate of African-American women is twice as high as that of white people (Gibbs, 2001). In addition, upper genital tract infections and/or inflammation are closely related factors to spontaneous preterm birth and premature delivery. The new point of view is that



the degree of close association between spontaneous preterm birth and premature delivery and tissue infection and/or inflammation and humoral inflammatory cytokine concentration depends on a single gene polymorphism that determines these cytokines in the mother and fetus. Tumor necrosis factor- α -308 (TNF- α -308), interleukin, and three gene polymorphisms of -1 β (IL-1 β) +3953/3954 and IL-6-174 are most closely associated with spontaneous preterm birth and premature delivery. Toll-like receptors are an important part of the innate immune system, which are also associated with spontaneous preterm birth and premature delivery. Therefore, the modern academic view holds that preterm infants are themselves a genetic susceptibility marker of cerebral palsy.

Cerebral Dysplasia

Brain hypoplasia is the exact cause of cerebral palsy, including: schizencephaly, familial cavitation, polymicrogyria, and brain variants, which usually has the clinical characteristics of non-syndromic cerebral palsy. In addition, some non-evolving changes, such as X-linked non-progressive cerebellar hypoplasia and cerebellopontine hypoplasia, are also associated with the performance of cerebral palsy (Nelson *et al.*, 2005). Special attention should be paid to agenesis corporis callosi (or dysplasia). When examination shows that patients with cerebral palsy have agenesis corporis callosi, it is most likely caused by brain dysplasia rather than birth injury. The American Academy of Neurology suggests that the standard cerebral palsy diagnosis process should include the following:

(1) Careful inquiry of medical history and physical examination: Medical history inquiry costs less money and is non-invasive, and often provides valuable information for the cause of disease. Family history of cerebral palsy in children is characterized by thrombosis / vascular accident, mental retardation / disability, seizures, neuromotor disorders, tumors, neurological disorders, joint contracture or limb rigidity, congenital anomalies, infertility, recurrent miscarriage or stillbirth, and adult neurodegenerative diseases;

(2) Neuroimaging examination: The brain of all cerebral palsy children should be scanned by MRI (Magnetic Resonance Imaging) first. The overall abnormal rate of MRI in patients with cerebral palsy is 70% to 90%. Accurate

neuroimaging findings can help clinicians quickly help to pin on the direction of major diagnostic categories, including genetic, metabolic, thrombotic, or hypoxic-ischemic encephalopathy;

(3) Genetic and metabolic tests: If no clear cause is found after the first and second steps of examination, targeted genetic diagnosis should be considered, including MeCP2 gene sequencing, chromosome 15 methylation detection, genomic hybridization comparison of chromosomes and gene sequences (e.g., combined mental retardation), and ARX technology genetic testing (e.g., mental retardation and/or especially infantile spasms). Even skin biopsy chromosome examination and genome sequencing need to be considered, if there is obvious pigment abnormality;

(4) Detection of thrombophilia, including the tests of coagulation factor Vleiden gene, MTHFR gene, prothrombin II gene, and serum homocysteine gene. If neuroimaging suggests a thrombotic event, the above gene tests shall be sure to be considered. Such tests should be targeted at all patients with cerebral palsy, and often require parental testing to identify the cause and estimate the risk of recurrence;

(5) Advanced metabolic disease and gene detection, including sulfite strips, plasma creatine and glycoamine levels, urine and serum uric acid levels, Bratton-Marshall screening, and L1 CAM gene detection.

Congenital Metabolic Disorder

A number of studies have long suggested that idiopathic cerebral palsy with unknown causes is associated with metabolic disorders, such as diseases with abnormal purine/pyrimidine metabolism (self-mutilation syndrome and its variants), hyperammonemia/urea circulatory disorders, 3-hydroxybutyrate deficiency, pyruvate dehydrogenase deficiency and other congenital lactic acidosis. These metabolic disorders are described as having a "non-hypoxic phenotype similar to hypoxic-ischemic encephalopathy." (Nelson, 2008) To determine whether these metabolic disorders are the causes of cerebral palsy, the following conditions should be met:

(1) There is no evidence of hypoxic-ischemic events before cerebral palsy;

(2) There is no deformity / special facial features;

(3) There is no biochemical abnormalities (such as hypoglycemia, hyperammonemia, electrolyte disorder);



- (4) There is no organ hypertrophy;
- (5) There is no macrocephaly;
- (6) There are no other signs or symptoms of inflammation.

However, in view of the fact that the simple and effective detection techniques for above metabolic disorders have not been developed and the detection rate is expect to be very low (1%), it is not recommended that metabolic disease screening should be conducted for cerebral palsy patients in a targeted manner. (Wang, 2004) It should be conducted only if specific indications are identified in the medical history, physical examination or laboratory data. For cases that meet the criteria of "non-hypoxic phenotype similar to hypoxic-ischemic encephalopathy" mentioned above, extra care should be taken, as invasive examination may be required and it may be very difficult. Therefore, unless there is a specific test to confirm the diagnosis, it is still very difficult to identify the cause of cerebral palsy.

Conclusions

In spite of the progress made over the past decade in detection methods for the intrauterine conditions of the fetus, the pregnant uterus is still a "black box" of potential genetic risk factor, pre-existing disease in the mother and accidental injury, and even advanced detection methods are still unable to accurately predict pregnancy outcomes (Zhang and Pan, 2000). Previously, mishandling of the perinatal period has been blamed for cerebral palsy. A large amount of undeniable evidence indicates that genetic factor is one of the important factors in the occurrence of cerebral palsy. Like most diseases of the nervous system, cerebral palsy presents a complex genetic predisposition (Xu *et al.*, 2002). To explore the interaction between certain pathogenic factors and genetic heterogeneity will become a new direction for future research on pathogenic factors of cerebral palsy.

References

Bodensteiner JB, Johnsen SD. Cerebellar injury in the extremely premature infant: newly recognized but

- relatively common outcome. *Journal of Child Neurology* 2005; 20(2): 139-42.
- Feng GQ, Shang XP, Lin XZ. Analysis of clinical symptoms of cerebral palsy and head CT. *Chinese Journal of Rehabilitation Theory and Practice* 2001; 7(4): 170-73.
- Gibbs RS. The relationship between infection and adverse pregnancy outcomes: an overview. *Annals of Periodontology* 2001; 6(1): 153-63.
- Hu YY. Development of the concept of cerebral palsy. *Chinese Journal of Rehabilitation Theory and Practice* 2003; 9(5): 257-58.
- Jacobsson B, Hagberg G. Antenatal risk factors for cerebral palsy. *Best Practice & Research Clinical Obstetrics & Gynaecology* 2004; 18(3): 425-36.
- Li S, Lin Q, Liu J. Prevalence of childhood cerebral palsy in six provinces in China. *National Medical Journal of China* 2001; 81(20): 1220-23.
- Lin S, Xu JM, Sun J, Li CY. MRI features of periventricular leukomalacia in children with cerebral palsy. *Chinese Journal of Rehabilitation Theory and Practice* 2001; 7(1): 21-22.
- Mutch LW, Alberman E, Hagberg B, Kodama K, Perat MV. Cerebral palsy epistemology: where are we now and where are we going. *Developmental Medicine & Child Neurology* 1992; 34: 547-55.
- Nelson KB, Dambrosia JM, Iovannisci DM, Cheng S, Grether JK, Lammer E. Genetic polymorphisms and cerebral palsy in very preterm infants. *Pediatric Research* 2005; 57(4): 484-99.
- Nelson KB. Causative factors in cerebral palsy. *Clinical Obstetrics & Gynecology* 2008; 15(1): 21-26.
- Raiu TN, Nelson KB, Ferriero D, Lynch JK. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. *Pediatrics* 2007; 120(3): 609-16.
- Schaefer GB. Genetics considerations in cerebral palsy. *Seminars in Pediatric Neurology* 2008; 15(1): 21-26.
- Velickovic M. Treatment of cerebral palsy in the past, nowadays and in the future. *Journal of Applied Clinical Pediatrics* 2003; 18(3): 158-59.
- Wang H. The Prevention research status of cerebral palsy. *Chinese Journal of Rehabilitation Medicine* 2004; 19(8): 637-40.
- Xu ZC, Sun YJ, Gao WY. The value of auxiliary examination for diagnosis of pediatric cerebral palsy. *Chinese Journal of Rehabilitation Theory and Practice* 2002; 8(1): 34-35.
- Zhang YL, Pan YQ. The diagnostic value of ventricular ultrasound in cerebral palsy. *Chinese Journal of Practical Pediatrics* 2000; 15(2): 108-10.
- Zhong YQ, Wu J, Wu KM, Wen R, Hou G, Peng D, Li X, Shuai H, Xie X, Tao X, Zhou W. Evaluation of risk factors associated with cerebral palsy in children of Leshan Prefecture, Sichuan: a case control study on 308 cases. *Chinese Journal of Preventive Medicine* 2002; 36(5): 323-26.

