DOI:10.4274/tnd.67864
Turk J Neurol 2018;24:1-2

Cerebral Palsy and Genetics

Serebral Palsi ve Genetik

Nihan Hande Akçakaya[1], Zuhal Yapıcı[2], Uğur Özbek[3]

[1]Spastic Children's Foundation of Turkey, Clinic of Neurology, Istanbul; Istanbul University Aziz Sancar Institute of Experimental Medicine, Department of Genetics, Istanbul, Turkey

[2]Istanbul University Istanbul Faculty of Medicine, Department of Neurology, Division of Child Neurology, Istanbul, Turkey

[3]Acibadem University Faculty of Medicine, Department of Medical Genetics, Istanbul, Turkey

Keywords: Cerebral palsy, genetics, spastic, ataxic, dyskinetic
Anahtar Kelimeler: Serebral palsi, genetik, spastik, ataksik, diskinetik

Cerebral Palsy and Genetics

Cerebral palsy (CP), is a permanent, but not progressive, postural and movement disorder caused by brain injury or dysgenesis during rapid brain development (1,2,3,4). The term CP describes consequences rather than causes, so it is not a true diagnosis. The etiology is different in every patient. Hereditary CP types are being described with the developing technology (2,3,4,5).

CP may involve static hereditary diseases and may also be confused with slowly-progressive genetic diseases (1,2). In this process, the first contribution of technology to neurology is imaging methods. The etiology of movement disorders can be understood with brain magnetic resonance imaging (MRI), and the time of brain damage can be predicted (2). However, at least one-fifth of patients with CP have normal or non-specific neuroimaging findings and at least 30% are thought to be inherited (3). The absence of MRI findings is as important as their presence. Among the diseases without MRI findings, dopa-responsive dystonia and slowly-progressive hereditary spastic paraparesis (HSP) can be confused with diparetic CP. Genetic testing is diagnostic in cases of clinical suspicion. Findings that have led to a further investigation of patients who are suspected of having CP are given in Table 1.

In CP-genetic association, it is important to keep in mind that along with the immature brain being vulnerable to trauma, genetic pathologies are more likely to be seen in cases of premature birth and hypoxia. Hereditary diseases, mainly chromosomal abnormalities, are prevalent in premature infants (3). Beneath neonatal asphyxia, there may be neuromuscular diseases such as Prader-Willi syndrome, congenital myotonic dystrophy, and many clinical conditions leading to hypotonia (1). Possible genetic factors should be investigated in patients with a history of premature birth or hypoxia who present with motor problems prior to the diagnosis of CP (1,4).

New genomic technologies have elucidated many neurodevelopmental patterns that could not be solved by MRI (2). Nowadays, diseases are reclassified in the direction of genetic and molecular bases (5). New diseases and syndromes are being defined by chromosomal microarray (MA) and next-generation sequencing (NGS) techniques. Genetic mechanisms discussed in the pathogenesis of CP are mitochondrial inheritance, copy number variation, epigenetic adaptation, and genomic variation/mutations (3).

In this case, how can new genomic technologies provide a better understanding of CP and enlighten its etiology? First, the association of variants with CP risk factors such as susceptibility to thrombosis, hemorrhage, and hypoxia can be investigated by genetic association studies. The predisposition is dependent on DNA variants and on epigenetic mechanisms affected by environmental factors and the polygenic/omnigenic effect of several minor effecting variants. Therefore, the candidate gene

Address for Correspondence/Yazışma Adresi: Nihan Hande Akçakaya MD, Spastic Children's Foundation of Turkey, Clinic of Neurology, Istanbul, Turkey
Phone: +90 533 541 36 33 E-mail: nhakcakaya@gmail.com ORCID ID: orcid.org/0000-0001-8414-4017
Received/Geliş Tarihi: 10.07.2017 **Accepted/Kabul Tarihi:** 02.08.2017

Table 1. Clinical and neuroimaging "red flags" that may require genetic testing in cerebral palsy
1. Normal MRI or movement disorder not correlated with lesion
2. Isolated globus pallidus involvement in MRI
3. Severe movement disorders without perinatal trauma
4. History of kinship and/or hereditary transition of the disease in pedigree
5. Dysmorphic findings despite a history consistent with CP
6. Hypotonia
7. Rigidity
8. Paraplegia
9. No correlations between motor involvement and mental involvement (minimal or no mental impairment despite tetraplegia or severe mental impairment despite minimal motor involvement)
10. Neurodevelopmental regression or progressive deterioration in symptoms

MRI: Magnetic resonance imaging, CP: Cerebral palsy.
*The table was modified from the article of Lee et al. (2).

or variant has not yet been identified (3). Secondly, it has been shown that MA can enlight account for 10-20% of CPs (3,4). Chromosomal MA is a new, high-resolution chromosome analysis technique. It can detect submicroscopic chromosomal losses and increases. In motor-mental retardation and autism spectrum disorders with or without congenital anomalies, MA is the first test to be performed together with classic karyotype analysis. It should be used in selected cases in neurologic phenotypes such as CP and epilepsy (2,4). Third, NGS methods can be used to diagnose rare and unknown genetic diseases by genome-wide sequencing (5). Whole-genome sequencing and whole-exome sequencing, in which coding regions are sequenced, were used initially for research but now they are regularly used. Epileptic encephalopathies and HSPs that can interfere with CP can be screened with NGS panels (4,5).

Genes responsible for spastic quadriplegic CP classified under hereditary CP are *KANK1, AP4E1, AP4M1, AP4B1*, and *AP4S1* (3,5). Mutations responsible for ataxic CP are found in the genes *KCNC3*, *ITPR1*, and *SPTBN2* (3). It should be remembered that there are genes waiting to be discovered under the heading of CP. Neurologists responsible for the diagnosis and treatment of neurologic diseases of all ages should know new genomic methods. Genetic diagnosis is essential for definite diagnosis, correct treatment, counseling, and preventive services.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.Y., U.Ö., Concept: N.H.A., Design: N.H.A., Data Collection or Processing: Z.Y., N.H.A., Analysis or Interpretation: U.Ö., N.H.A., Literature Search: U.Ö., N.H.A., Writing: N.H.A.

Conflict of Interest: The authors have reported no conflicts of interest.

Financial Disclosure: The authors have nothing to disclose.

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