Microcephaly, seizures, and developmental delay

Description

Microcephaly, seizures, and developmental delay (MCSZ) is a condition characterized by an abnormally small head size (microcephaly) and neurological problems related to impaired brain development before birth. Affected individuals typically have recurrent seizures (epilepsy) beginning in infancy and delayed development of motor skills, such as sitting and walking. Speech is also delayed, and some affected individuals are never able to speak. Intellectual disability and behavior problems, primarily hyperactivity, are also common features of MCSZ. Rarely, individuals with MCSZ also have poor balance and coordination (ataxia).

Frequency

MCSZ is a rare disorder. Its prevalence is unknown.

Causes

MCSZ is caused by mutations in the *PNKP* gene. This gene provides instructions for making an enzyme that is critical for repairing broken DNA strands. DNA breaks may be caused by potentially harmful molecules (such as reactive oxygen species) produced during normal cellular functions, natural and medical radiation, or other environmental exposures. They may also occur when chromosomes exchange genetic material in preparation for cell division. At the site of damage, the PNKP enzyme modifies the broken ends of the DNA strands so that they can be joined back together.

PNKP gene mutations lead to production of an unstable enzyme that is quickly broken down in the cell. Shortage of the PNKP enzyme prevents efficient repair of damaged DNA. Nerve cells seem especially susceptible to such damage. It is thought that DNA damage that accumulates during development before birth leads to the death of nerve cell precursors, impairing normal brain growth and causing microcephaly and the other neurological features of MCSZ.

Accumulated DNA damage in nerve cells in the brain after birth, particularly the part that coordinates movement (the cerebellum), likely underlies ataxia. It is unclear why some people have cerebellar nerve degeneration after birth in addition to impaired brain development before birth and others do not. Researchers suspect that additional genetic factors play a role.

Learn more about the gene associated with Microcephaly, seizures, and developmental delay

- PNKP

Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- EIEE10
- Epileptic encephalopathy, early infantile, 10
- MCSZ

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Microcephaly, seizures, and developmental delay (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3150667/)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- MICROCEPHALY, SEIZURES, AND DEVELOPMENTAL DELAY; MCSZ (https://omim.org/entry/613402)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28MCSZ%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

References

- Dumitrache LC, McKinnon PJ. Polynucleotide kinase-phosphatase (PNKP) mutationsand neurologic disease. Mech Ageing Dev. 2017 Jan;161(Pt A):121-129. doi:10.1016/j.mad.2016.04.009. Epub 2016 Apr 26. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/27125728) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5161711/)
- Poulton C, Oegema R, Heijsman D, Hoogeboom J, Schot R, Stroink H, WillemsenMA, Verheijen FW, van de Spek P, Kremer A, Mancini GM. Progressive cerebellaratrophy and polyneuropathy: expanding the spectrum of PNKP mutations. Neurogenetics. 2013 Feb;14(1):43-51. doi: 10.1007/s10048-012-0351-8. Epub 2012Dec 9. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23224214)
- Reynolds JJ, Walker AK, Gilmore EC, Walsh CA, Caldecott KW. Impact of PNKPmutations associated with microcephaly, seizures and developmental delay onenzyme activity and DNA strand break repair. Nucleic Acids Res. 2012Aug;40(14): 6608-19. doi: 10.1093/nar/gks318. Epub 2012 Apr 15. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22508754) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413127/)
- Shen J, Gilmore EC, Marshall CA, Haddadin M, Reynolds JJ, Eyaid W, Bodell A, Barry B, Gleason D, Allen K, Ganesh VS, Chang BS, Grix A, Hill RS, Topcu M, Caldecott KW, Barkovich AJ, Walsh CA. Mutations in PNKP cause microcephaly, seizures and defects in DNA repair. Nat Genet. 2010 Mar;42(3):245-9. doi:10.1038/ng.526. Epub 2010 Jan 31. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20118933) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835984/)
- Shimada M, Dumitrache LC, Russell HR, McKinnon PJ. Polynucleotidekinase-phosphatase enables neurogenesis via multiple DNA repair pathways tomaintain genome stability. EMBO J. 2015 Oct 1;34(19):2465-80. doi:10.15252/embj.201591363. Epub 2015 Aug 19. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/26290337) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4601665/)
- Weinfeld M, Mani RS, Abdou I, Aceytuno RD, Glover JN. Tidying up loose ends:the role of polynucleotide kinase/phosphatase in DNA strand break repair. TrendsBiochem Sci. 2011 May;36(5):262-71. doi: 10.1016/j.tibs.2011.01.006. Epub 2011Feb 25. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21353781) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3134258/)

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