Riboflavin transporter deficiency neuronopathy

Description

Riboflavin transporter deficiency neuronopathy is a disorder that affects nerve cells (neurons). Affected individuals typically have hearing loss caused by nerve damage in the inner ear (sensorineural hearing loss) and signs of damage to other nerves.

In addition to nerves in the inner ear, riboflavin transporter deficiency neuronopathy involves nerves found in the part of the brain that is connected to the spinal cord (the brainstem), specifically in a region of the brainstem known as the pontobulbar region. Damage to these nerves causes paralysis of the muscles controlled by them, a condition called pontobulbar palsy. Nerves in the pontobulbar region help control several voluntary muscle activities, including breathing, speaking, and moving the limbs. As a result of pontobulbar palsy, people with riboflavin transporter deficiency neuronopathy can have breathing problems; slurred speech; and muscle weakness in the face, neck, shoulders, and limbs. Affected individuals can also have muscle stiffness (spasticity) and exaggerated reflexes.

The age at which riboflavin transporter deficiency neuronopathy begins varies from infancy to young adulthood. When the condition begins in infancy, the first symptom is often breathing problems caused by nerve damage, which can be life-threatening. When the condition begins in children or young adults, sensorineural hearing loss usually occurs first, followed by signs of pontobulbar palsy.

If not treated, the signs and symptoms of riboflavin transporter deficiency neuronopathy worsen over time. Severe breathing problems and respiratory infections are the usual cause of death in people with this condition. Without treatment, affected infants typically survive less than one year. However, those who develop the condition after age 4 often survive more than 10 years.

Riboflavin transporter deficiency neuronopathy encompasses two conditions that were once considered distinct disorders: Brown-Vialetto-Van Laere syndrome (BVVLS) and Fazio-Londe disease. The two conditions have similar signs and symptoms, but Fazio-Londe disease does not include sensorineural hearing loss. Because these two conditions share a genetic cause and have overlapping features, researchers determined that they are forms of a single disorder.

Frequency

Riboflavin transporter deficiency neuronopathy is a rare condition. Approximately 100 cases have been reported in the scientific literature.

Causes

Riboflavin transporter deficiency neuronopathy is caused by mutations in the *SLC52A2* or *SLC52A3* gene. These genes provide instructions for making related proteins called riboflavin transporters: RFVT2 is produced from the *SLC52A2* gene, and RFVT3 is produced from the *SLC52A3* gene. Both proteins move (transport) a vitamin called riboflavin (also called vitamin B_2) across the cell membrane. Riboflavin cannot be made by the body, so it must be obtained from the food a person eats. The RFVT3 protein is found at especially high levels in cells of the small intestine and is important for absorbing riboflavin during digestion so that the vitamin can be used in the body. The RFVT2 protein is found in cells of the brain and spinal cord and is important for ensuring that these tissues have enough riboflavin for proper functioning.

In the cells of the body, riboflavin is the core component of molecules called flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). FAD and FMN are involved in many different chemical reactions and are required for a variety of cellular processes. One important role of these molecules is in the production of energy for cells. FAD and FMN are also involved in the breakdown (metabolism) of carbohydrates, fats, and proteins.

Mutations in the *SLC52A2* or *SLC52A3* gene lead to an abnormal riboflavin transporter protein with impaired ability to transport riboflavin. Consequently, there is a reduction of riboflavin available in the body. However, it is unclear how these changes lead to the nerve problems characteristic of riboflavin transporter deficiency neuronopathy.

Learn more about the genes associated with Riboflavin transporter deficiency neuronopathy

- SLC52A2
- SLC52A3

Inheritance

Riboflavin transporter deficiency neuronopathy usually follows an autosomal recessive pattern of inheritance, 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

- Brown-Vialetto-Van Laere syndrome

- BVVLS
- Fazio-Londe disease
- Fazio-Londe syndrome
- Pontobulbar palsy with deafness
- Progressive bulbar palsy with sensorineural deafness
- Riboflavin transporter deficiency

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Brown-Vialetto-van Laere syndrome 1 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0796274/)

Genetic and Rare Diseases Information Center

- Riboflavin transporter deficiency (https://rarediseases.info.nih.gov/diseases/9993/index)

Patient Support and Advocacy Resources

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

Catalog of Genes and Diseases from OMIM

- BROWN-VIALETTO-VAN LAERE SYNDROME 1; BVVLS1 (https://omim.org/entry/211530)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28brown-vialetto-van+laere+syndrome%5BTIAB%5D%29+OR+%28bvvls%5BTIAB%5D%29+OR+%28pontobulbar+palsy+with+deafness%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

References

- Bosch AM, Abeling NG, Ijlst L, Knoester H, van der Pol WL, Stroomer AE,Wanders RJ, Visser G, Wijburg FA, Duran M, Waterham HR. Brown-Vialetto-Van Laereand Fazio Londe syndrome is associated with a riboflavin transporter defectmimicking mild MADD: a new inborn error of metabolism with potential treatment. JInherit Metab Dis. 2011 Feb;34(1):159-64. doi: 10.1007/s10545-010-9242-z. Epub2010 Nov

26. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21110228) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3026695/)

- Bosch AM, Stroek K, Abeling NG, Waterham HR, Ijlst L, Wanders RJ. TheBrown-Vialetto-Van Laere and Fazio Londe syndrome revisited: natural history,genetics, treatment and future perspectives. Orphanet J Rare Dis. 2012 Oct29;7:83. doi: 10.1186/1750-1172-7-83. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23107375) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3517535/)
- Cali E, Dominik N, Manole A, Houlden H. Riboflavin Transporter Deficiency.2015 Jun 11 [updated 2021 Apr 8]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews(R)[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Availablefrom http://www.ncbi.nlm.nih.gov/books/NBK299312/ Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/26072523)
- Dipti S, Childs AM, Livingston JH, Aggarwal AK, Miller M, Williams C, Crow YJ. Brown-Vialetto-Van Laere syndrome; variability in age at onset and diseaseprogression highlighting the phenotypic overlap with Fazio-Londe disease. BrainDev. 2005 Sep;27(6):443-6. doi: 10.1016/j.braindev.2004.10.003. Epub 2004 Dec 15. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16122634)
- Foley AR, Menezes MP, Pandraud A, Gonzalez MA, Al-Odaib A, Abrams AJ, SuganoK, Yonezawa A, Manzur AY, Burns J, Hughes I, McCullagh BG, Jungbluth H, Lim MJ,Lin JP, Megarbane A, Urtizberea JA, Shah AH, Antony J, Webster R, Broomfield A,Ng J, Mathew AA, O'Byrne JJ, Forman E, Scoto M, Prasad M, O'Brien K, Olpin S,Oppenheim M, Hargreaves I, Land JM, Wang MX, Carpenter K, Horvath R, Straub V,Lek M, Gold W, Farrell MO, Brandner S, Phadke R, Matsubara K, McGarvey ML,Scherer SS, Baxter PS, King MD, Clayton P, Rahman S, Reilly MM, Ouvrier RA,Christodoulou J, Zuchner S, Muntoni F, Houlden H. Treatable childhoodneuronopathy caused by mutations in riboflavin transporter RFVT2. Brain. 2014Jan;137(Pt 1):44-56. doi: 10.1093/brain/awt315. Epub 2013 Nov 19. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/24253200) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3891447/)
- Green P, Wiseman M, Crow YJ, Houlden H, Riphagen S, Lin JP, Raymond FL, ChildsAM, Sheridan E, Edwards S, Josifova DJ. Brown-Vialetto-Van Laere syndrome, aponto-bulbar palsy with deafness, is caused by mutations in c20orf54. Am J HumGenet. 2010 Mar 12;86(3):485-9. doi: 10.1016/j.ajhg.2010.02.006. Epub 2010 Mar 4. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20206331) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2833371/)
- Haack TB, Makowski C, Yao Y, Graf E, Hempel M, Wieland T, Tauer U, Ahting U, Mayr JA, Freisinger P, Yoshimatsu H, Inui K, Strom TM, Meitinger T, Yonezawa A, Prokisch H. Impaired riboflavin transport due to missense mutations in SLC52A2causes Brown-Vialetto-Van Laere syndrome. J Inherit Metab Dis. 2012Nov; 35(6):943-8. doi: 10.1007/s10545-012-9513-y. Epub 2012 Aug 3. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22864630) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3470687/)

- Johnson JO, Gibbs JR, Megarbane A, Urtizberea JA, Hernandez DG, Foley AR, Arepalli S, Pandraud A, Simon-Sanchez J, Clayton P, Reilly MM, Muntoni F, Abramzon Y, Houlden H, Singleton AB. Exome sequencing reveals riboflavintransporter mutations as a cause of motor neuron disease. Brain. 2012 Sep; 135(Pt9):2875-82. doi: 10.1093/brain/aws161. Epub 2012 Jun 26. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22740598) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437022/)
- Nabokina SM, Subramanian VS, Said HM. Effect of clinical mutations onfunctionality of the human riboflavin transporter-2 (hRFT-2). Mol Genet Metab. 2012 Apr;105(4):652-7. doi: 10.1016/j.ymgme.2011.12.021. Epub 2012 Jan 5. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/22273710) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3309148/)
- Oregon State University Linus Pauling Institute: Riboflavin (https://lpi.oregonstate.edu/mic/vitamins/riboflavin)

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