Liddle Syndrome

Subjects: Genetics & Heredity
Contributor: Camila Xu

Liddle syndrome is an inherited form of high blood pressure (hypertension).

Keywords: genetic conditions

1. Introduction

Liddle syndrome is characterized by severe hypertension that begins unusually early in life, often in childhood, although some affected individuals are not diagnosed until adulthood. Some people with Liddle syndrome have no additional signs or symptoms, especially in childhood. Over time, however, untreated hypertension can lead to heart disease or stroke, which may be fatal.

In addition to hypertension, affected individuals can have low levels of potassium in the blood (hypokalemia). Signs and symptoms of hypokalemia include muscle weakness or pain, fatigue, constipation, or heart palpitations. The shortage of potassium can also raise the pH of the blood, a condition known as metabolic alkalosis.

2. Frequency

Liddle syndrome is a rare condition, although its prevalence is unknown. The condition has been found in populations worldwide.

3. Causes

Liddle syndrome is caused by mutations in the *SCNN1B* or *SCNN1G* gene. Each of these genes provides instructions for making a piece (subunit) of a protein complex called the epithelial sodium channel (ENaC). These channels are found at the surface of certain cells called epithelial cells in many tissues of the body, including the kidneys, where the channels transport sodium into cells.

In the kidney, ENaC channels open in response to signals that sodium levels in the blood are too low, which allows sodium to flow into cells. From the kidney cells, this sodium is returned to the bloodstream (a process called reabsorption) rather than being removed from the body in urine.

Mutations in the *SCNN1B* or *SCNN1G* gene change the structure of the respective ENaC subunit. The changes alter a region of the subunit that is involved in signaling for its breakdown (degradation) when it is no longer needed. As a result of the mutations, the subunit proteins are not degraded, and more ENaC channels remain at the cell surface. The increase in channels at the cell surface abnormally increases the reabsorption of sodium (followed by water), which leads to hypertension. Reabsorption of sodium into the blood is linked with removal of potassium from the blood, so excess sodium reabsorption leads to hypokalemia.

3.1. The genes associated with Liddle syndrome

- SCNN1B
- SCNN1G

4. Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

5. Other Names for This Condition

- pseudoaldosteronism
- pseudoprimary hyperaldosteronism

References

1. Bogdanović R, Kuburović V, Stajić N, Mughal SS, Hilger A, Ninić S, Prijić S,Ludwig M. Liddle syndrome in a Serbian family and literature review of underlyingmutations. Eur J Pediatr. 2012 Mar;171(3):471-8. doi: 10.1007/s00431-011-1581-8.
2. Corvol P. Liddle's syndrome: heritable human hypertension caused by mutations in the Beta subunit of the epithelial sodium channel. J Endocrinol Invest. 1995Jul-Aug;18(7):592-4.
3. Hansson JH, Nelson-Williams C, Suzuki H, Schild L, Shimkets R, Lu Y, CanessaC, Iwasaki T, Rossier B, Lifton RP. Hypertension caused by a truncated epithelialsodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. NatGenet. 1995 Sep;11(1):76-82.
4. Hansson JH, Schild L, Lu Y, Wilson TA, Gautschi I, Shimkets R, Nelson-WilliamsC, Rossier BC, Lifton RP. A de novo missense mutation of the beta subunit of the epithelial sodium channel causes hypertension and Liddle syndrome, identifying a proline-rich segment critical for regulation of channel activity. Proc Natl Acad Sci U S A. 1995 Dec 5;92(25):11495-9.
5. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell. 2001 Feb 23;104(4):545-56. Review.
6. Rotin D. Role of the UPS in Liddle syndrome. BMC Biochem. 2008 Oct 21;9 Suppl 1:S5. doi: 10.1186/1471-2091-9-S1-S5. Review.
7. Schild L, Lu Y, Gautschi I, Schneeberger E, Lifton RP, Rossier BC.Identification of a PY motif in the epithelial Na channel subunits as a targetsequence for mutations causing channel activation found in Liddle syndrome. EMBO J. 1996 May 15;15(10):2381-7.
8. Smith JH, Lindor NM, Rabinstein AA. Cerebrovascular consequences ofpseudohyperaldosteronism. J Clin Hypertens (Greenwich). 2012 Aug;14(8):547-52.doi: 10.1111/j.1751-7176.2012.00639.x.
9. Snyder PM, Price MP, McDonald FJ, Adams CM, Volk KA, Zeiher BG, Stokes JB,Welsh MJ. Mechanism by which Liddle's syndrome mutations increase activity of ahuman epithelial Na+ channel. Cell. 1995 Dec 15;83(6):969-78.
10. Staub O, Dho S, Henry P, Correa J, Ishikawa T, McGlade J, Rotin D. WW domains of Nedd4 bind to the proline-rich PY motifs in the epithelial Na+ channel deletedin Liddle's syndrome. EMBO J. 1996 May 15;15(10):2371-80.
11. Warnock DG. Liddle syndrome: genetics and mechanisms of Na+ channel defects.Am J Med Sci. 2001 Dec;322(6):302-7. Review.