



JOUBERT SYNDROME &
RELATED DISORDERS FOUNDATION

The faith to believe, the hope to dream, the love to see it through

Juvenile Nephronophthisis with cerebellar malformation

Juvenile nephronophthisis refers to a disorder in which there is a particular form of renal insufficiency. In some individuals, juvenile nephronophthisis can occur as part of a group of genetic conditions that result from an abnormality in the part of the brain called the cerebellar vermis. The disorders that share this cerebellar malformation are known as Joubert syndrome and related disorders (JSRD). These conditions have some characteristics in common, but there is a spectrum of symptoms and abilities in affected individuals. For additional information regarding this family of conditions, please refer to the Joubert Syndrome & Related Disorders Foundation website at www.jsrdf.org.

Individuals diagnosed with juvenile nephronophthisis traditionally exhibit the following features:

- Renal insufficiency, particularly nephronophthisis. Initial symptoms of nephronophthisis include increased drinking and urination, and sometimes anemia (low blood count). Increased production of large amounts of urine or new onset of bed-wetting or incontinence is common in affected individuals.
- Kidney failure usually develops in childhood or early adulthood, by an average age of 13 years, and requires dialysis or transplantation.

While less common, the following features may also be present in some individuals:

- Underdevelopment (hypoplasia) or complete lack (aplasia/agenesis) of the cerebellar vermis, usually indicated by the “Molar Tooth” sign found on an axial view of a brain MRI scan.
- About 10% of individuals with nephronophthisis develop retinal dystrophy, which may be diagnosed by increased pigmentation of the retina or flattened electroretinogram (ERG) traces. The combination of nephronophthisis and retinal dystrophy is termed Senior-Løken syndrome (see separate information sheet for additional details)
- Oculomotor apraxia (OMA), which is a specific eye movement abnormality in which it is difficult for children to track objects smoothly. Eyes may appear to jump, with jerky eye movements.
- Developmental delays/mental retardation—variable severity. Most individuals with juvenile nephronophthisis alone do not have any developmental delays.
- Difficulty coordinating voluntary muscle movements; uncoordinated movements (ataxia)
- Decreased muscle tone (hypotonia)
- Abnormal breathing pattern with episodes of rapid breathing or panting (hyperpnea), which may be followed by pauses in breathing (apnea).
- Facial features may be abnormal in appearance (eyes far set from each other, small ear lobes, broad forehead, arched eyebrows, broad mouth)
- Vascular hypertension, as a result of the affected kidneys.
- Difficulty processing and reacting to information received through any of their five senses.
- Other conditions not listed here may also be observed

Explanation of features:

Some individuals diagnosed with juvenile nephronophthisis may have an absence or underdevelopment of part of the brain called the cerebellum vermis which controls balance and coordination. The severity of the resulting ataxia (uncoordinated movements) varies from person to person. Some individuals with juvenile nephronophthisis will not have any cerebellar abnormalities or ataxia.

Decreased muscle tone occurs in some children with this form of juvenile nephronophthisis. As a result of the poor muscle tone, developmental delay (usually in gross motor, fine motor and speech areas) is common. Developmental delays, when present, are usually treated through physical therapy, occupational therapy, speech therapy, and infant stimulation. Most children diagnosed with this form of juvenile nephronophthisis are able to achieve standard milestones, although some may do so at a later age.

Some individuals may experience difficulties resulting from an inability to appropriately process information received through the five senses - hearing, seeing, tasting, touching, and smelling - as well as from their poor sense of balance

and muscle movement. Some families have found that sensory integration therapy can help to minimize these sensory issues.

Mild to moderate mental retardation may occur, but overall health and growth are not known to be severely affected by this condition unless kidney failure occurs.

Renal insufficiency known as juvenile nephronophthisis may develop during childhood. Initial symptoms may include excessive thirst and urination, and kidney failure may result. Individuals diagnosed with juvenile nephronophthisis typically produce large amounts of urine. This may be noted early in life and may result in the production of large amounts of urine throughout the day and bedwetting at night. An unusually dilute urine sample obtained upon waking can be an early clue to this diagnosis.

Management and treatment:

Presently, there is no cure for juvenile nephronophthisis. It is recommended that affected individuals see the appropriate specialists necessary to help monitor their various clinical features. Suggested specialists include a nephrologist (kidney specialist), ophthalmologist (eye doctor), geneticist and neurologist, as well as any others recommended by your doctor.

Screening for some of the complications associated with juvenile nephronophthisis, such as those related to vision or kidney involvement that may become progressive over time, is recommended on an annual basis. Kidney failure usually develops in childhood or early adulthood, and management may require medications, dialysis, and/or renal transplantation. Retinal dystrophy may not have onset until after age 10 years. Please refer to the Joubert Syndrome Foundation and Related Cerebellar Disorders website's "Evaluation Recommendations" link for a complete listing of recommended annual tests.

Inheritance and recurrence:

Juvenile nephronophthisis is passed down from parents to offspring as an autosomal recessive trait, which means that both parents have one altered copy of the gene responsible for this disorder in their DNA. (In order for a child to be born with this disorder, both the egg and the sperm must contain the same altered gene in question). The odds of having a child born with juvenile nephronophthisis to parents who carry the altered gene involved are 1 in 4, or 25%, in each pregnancy that they share.

Genetic cause:

Several genes responsible for juvenile nephronophthisis have been identified, including *NPHP1*, *NPHP3*, and *NPHP4*. Deletions and/or mutations in *NPHP1* have been identified in ~30% of those with juvenile nephronophthisis, with or without cerebellar or other features. In addition, the *AHI1* and *CEP290* genes are associated with Joubert syndrome and complications of retinal dystrophy and/or nephronophthisis. However, these do not explain all cases of juvenile nephronophthisis, and the genetics of this disorder remain complex. It is likely that other genes that cause this condition exist.

Research is currently underway to assist medical professionals in developing a greater understanding about this disorder. For more information about genetic research, please contact the Joubert Syndrome and Related Disorders Foundation.

Additional resources for families:

- Joubert Syndrome and Related Disorders Foundation: www.jsrdf.org
- National Kidney Foundation: www.kidney.org

Resources used in the creation of this document:

- Gleeson, J.G. et al. (2003). Molar Tooth Sign of the Midbrain-Hindbrain Junction: Occurrence in Multiple Distinct Syndromes. *American Journal of Medical Genetics*, 125A, 125-134.
- Parisi, M, et al. (2004). The NPHP1 Gene Deletion Associated with Juvenile Nephronophthisis Is Present in a Subset of Individuals with Joubert Syndrome. *American Journal of Human Genetics*, 75, 82-91.
- Parisi, M.A. and Glass, I. A. "Joubert Syndrome" GeneReviews, Online publication of expert-authored disease reviews: www.genereviews.org
- Satran, D, Pierpont, M. M., & Dobyns, W. B. (1999). Cerebello-Oculo-Renal Syndromes Including Arima, Senior-Loken, and COACH Syndromes: More Than Just Variants of Joubert Syndrome. *American Journal of Medical Genetics*, 86, 459-469.

The information presented is intended to summarize this condition as it is presently understood by medical professionals. The statements included in this document are for information only and should not be considered as medical advice. Please always consult your physician for medical advice.