Volume 7 Issue 2 2021

ISSN 2454-3055

**INTERNATIONAL
JOURNAL OF
ZOOLOGICAL
INVESTIGATIONS**

***Forum for Biological and
Environmental Sciences***

Published by Saran Publications, India

Nephronophthisis and its Impact on Human Body: A Review

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Received: 9th November, 2021; **Accepted:** 8th December, 2021; **Published online:** 14th December, 2021

<https://doi.org/10.33745/ijzi.2021.v07i02.080>

Abstract: Nephronophthisis (NPHP) is an autosomal cystic kidney disease which is the most common hereditary disease. It is caused by mutations in 11 genes, known as nephrocystins (NPHP1-11, NPHP1L). With the identification of an increasing number of these genes, our knowledge of nephronophthisis changes and improves our comprehension of the pathomechanisms of NPHP. Ciliary expression of nephrocystins with other cystoproteins, such as polycystins 1 and 2, and fibrocystins have been documented in recent studies. These findings have directed our emphasis towards a pathomechanism with ciliary (ciliopathy) and planar cell polarity abnormalities (PCP). Furthermore, novel nephrocystin genes have been found to cause considerably larger than predicted illness spectrum of NPHP. In the same NPHP gene, various mutations might cause varied severity of the illness. In this study, we discuss about NPHP pathomechanisms and highlight the clinical heterogeneity of the illness. With the potential of oligogenicity in NPHP, the clinical range has grown even more complicated.

Keywords: Nephronophthisis, Renal disease, Kidney problems, Anaemia

Citation: Ashok K., Babu M. and Pugazharasan P.: Nephronophthisis and its impact on human body: A review. Intern. J. Zool. Invest. 7 (2): 898-901, 2021.

<https://doi.org/10.33745/ijzi.2021.v07i02.080>

Introduction

The nephronophthisis is a kidney disease. Inflammation and scarring (fibrosis) affects the function of the kidney (Steele *et al.*, 1980). These disorders lead to increased urine output (polyuria) and an excess of thirst (polydipsia) (fatigue) (Zollinger *et al.*, 1980; Waldherr *et al.*, 1982; Hildebrandt *et al.*, 1992, 1997; Blowey *et al.*, 1996). Moreover, fluid-filled cysts are formed in the kidneys, generally in a location known as the corticomedullary zone. A decrease in Red Blood Cells, a disease known as anaemia, is another

characteristic of nephronophthisis (Haider *et al.*, 1998). Nephronophthisis eventually leads to a renal disease at the end of stage (ESRD), a life-threatening kidney failure that happens when the kidneys can no longer filter fluids and bodily waste (Omran *et al.*, 2000). The approximate age at which ESRD starts can be described as -- around 1 age (baby), around 13 age (young) and about 19 age (adolescent). About 85% of nephronophthisis patients are solitary thus they do not have any other indications or symptoms (Hildebrandt and

Omran, 2001). There are further characteristics of some persons with nephronophthisis, including liver fibroses, heart defects, or reverse image of the location of one or more organs within the body (situs inversus) (Mollet *et al.*, 2002). Nephronophthisis may be part of other syndromes, generally referred to as nephronophthises-associated ciliopathies, which have an effect on other parts of your body (Olbrich *et al.*, 2003). For example, a combination of nephronophthisis and a breakdown of light-sensitive tissue at the back of the eye (retinal degeneration), is characteristic of the Senior-Løken syndrome; a Joubert syndrome affects several body parts, causing neurological issues and other characteristics which may include nephronophthisis (Parisi *et al.*, 2004).

Frequency:

In worldwide populations, nephronophthisis is present (Saunier *et al.*, 2005). It is estimated in Canada as 1 in 50,000 births, in Finland at 1 in 100,000, and in the United States at 1 in 922,000. Its effects are unknown in other populations. In children and young adults, nephronophthisis is the most prevalent hereditary cause of ESRD (Hildebrandt and Zhou, 2007).

Causes:

There are numerous hereditary origins of nephronophthisis which are used to divide the disorder into different kinds (Salomon *et al.*, 2009). Kind 1 nephronophthisis, the most frequent type and cause of juvenile nephronophthisis, arises from the NPHP1 gene alterations (O'Toole *et al.*, 2010). NPHP-1 proteins and the other nephronophthisis-induced genes are known or suspected of playing functions in cell structures known as cilia (Wolf and Hildebrandt, 2011). Cilia are finger-like, tiny projections sticking out from the cell surface and involving the chemical signalling process. The structure and functional function of numerous cell and tissues, including cells in the kidney, liver, brain and the luminous tissue behind the eye, is crucial for cilia (the retina) (Benzing and Schermer, 2012).

Nephronophthisis genetic mutations are considered to affect the form or function of cilia, which will probably interfere with major chemical signals throughout development. While the scientists think that faulty cilia leads to nephronophthisis, the system remains uncertain. It is not understood why some patients with gene-associated mutations just have renal issues whereas others acquire other symptoms and indications (Hoff *et al.*, 2013).

Inheritance:

This disease inherits a recessive autosomal pattern that implies both copies of the gene which contain mutations in each cell (Srivastava and Sayer, 2014). The parents of a person with autosomal recession each have one copy of the defective gene, although they generally have no signs and symptoms (Wolf, 2015).

Treatment:

No cure for NPHP and its associated ciliopathies is currently available. Clinicians must concentrate on optimising the treatment of renal substitution, ideally when possible with renal transplantation (Stokman *et al.*, 2016). However, the future is more optimistic with a better knowledge of NPHP's pathophysiology (Konig *et al.*, 2017). Various medicines have demonstrated in recent years to be efficacious in decreasing renal cysts in animal models of NPHP and ADPKD including the vasopressin receptor antagonists, mTOR (mammalian rapamycin target), triptolid and roscovitine (cyclin-dependent kinase inhibitor) (Luo and Tao, 2018). Many of these medicines have been used recently in adult clinical trials. Furthermore, in zebrafish models of ciliopathy, several chemicals that may be possible treatments are tested (Larrue *et al.*, 2020).

Conclusion

In the past several years there has been considerable progress in the understanding of molecular genetics of NPHP. The heterogeneity, pleiotropic character of mutations and oligogenicity are rapidly becoming apparent to us

and all these add to NPHP's complexity. Further, hints to its pathophysiology are justified for identifying other NPHP genes that may be "ciliar." This requires cross-discipline collaboration on the worldwide screening of candidate genes in the animal and cell models, to sequence patient cohorts that lack current molecular diagnostics. Recognition of the unknown genetic cause in 70% of cases of NPHP, combined with an awareness of a recent identification of an NPHP-like phenotype in the mitochondrial gene XPNPEP3, may encourage the consideration of other nonciliar candidates, for example genes involved in cell contacts and in cytoskeleton. Ultimately, a protein and cell physiological understanding of the results should help to establish new treatment goals for the patients concerned and to treat them.

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