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Senior-Loken and other Renal-Retinal Syndromes: A Case Report and Review

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Abstract

Nephronophthisis (NPHP) is an autosomal recessive kidney disorder characterized by chronic tubulointerstitial nephritis that progresses eventually to end-stage kidney disease (ESKD). NPHP is often a part of a multisystem disorder such as Senior-Loken syndrome, Joubert syndrome, Senior-Boichis syndrome, Saldino-Mainzer syndrome, COACH syndrome, Arima syndrome, Alstrom syndrome, RHYNS syndrome and Jeune's dystrophy with several associated extra renal manifestations. Positional cloning of nine genes (NPHP1-9) as mutated in NPHP and characterization of their coded proteins have contributed to the concept of "ciliopathies". The ciliary theory explains the multiple organ involvement in NPHP that may manifest as retinitis pigmentosa, liver fibrosis, ataxia, and mental retardation. The treatment of choice for ESKD due to NPHP is kidney transplantation. Positional cloning of additional genes of NPHP will elucidate further signaling mechanisms and pathways that are involved, thereby opening new potential therapeutic approaches.

Keywords: Nephronophthisis, Ciliopathy, Chronic Tubulointerstitial Nephritis, Joubert Syndrome, End-Stage Kidney Disease

Introduction

Senior-Loken syndrome (SLS) is nephronophthisis (NPHP) and retinal dystrophy and was first described by Contreras, Senior (1), and Loken (2) in 1961. NPHP represents the most frequent genetic cause of end-stage kidney disease (ESKD) in the first three decades of life (3). NPHP is an autosomal recessive kidney disorder characterized by chronic tubulointerstitial nephritis that leads to ESKD. NPHP can be a part of several multisystem disorders and SLS accounts for about 10-15 % of cases of NPHP (4). Affected individuals invariably progress to ESKD, usually before the age of 20 years (1). We present a case of SLS and a brief overview of the various associated renal-retinal syndromes.

Case report

Our patient is a 12 year old girl who complained of generalized weakness, decreased appetite, nausea, and fatigue for 3 weeks. She also had night vision problems and was diagnosed with pigmentary retinopathy two years earlier. Review of systems was positive for polyuria, polydipsia for the preceding 1.5 years and severe learning difficulties. Family history was unknown as the child was adopted. The physical

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exam revealed a girl of short stature (she was in the 30th percentile for height and weight) with no nystagmus, negative pupillary reflexes and normal blood pressure. Fundoscopic exam by ophthalmology was positive for mottling of the retinal pigment epithelium and waxy pallor of the optic nerve head with attenuation of the retinal vessels. Lungs were clear; there was no pedal edema. The remainder of the physical exam was unremarkable. Upon evaluation laboratory studies revealed: Blood urea nitrogen (BUN) 174 mg/dl; creatinine, 21.6mg/dl; total CO_2, 11 mmol/L; sodium, 149 meq/L; chloride, 99 mmol/L; hemoglobin, 5.0 g/dl; and hematocrit, 13.6 % with normal leukocyte, platelet counts and liver enzymes. Initial urinanalysis (UA) revealed 2+ protein, 2+ blood, 10-12 white cells/hpf and bacteria but a repeat early morning UA showed a specific gravity of 1.015, +1 protein and no blood or red cell casts. Arterial blood gas showed a PO_2 of 87, PCO_2 of 26.7, HCO_3 19 and pH of 7.23 on room air. Abdominal ultrasound showed bilateral hyper-echogenic kidneys. The liver and spleen were normal. Electroretinography (ERG) demonstrated a rod response b-wave 10% of normal, a cone response b-wave 75% of normal amplitude and delayed implicit time. The amplitude of 30 Hz flicker responses was also reduced and the dark adapted final threshold was elevated at 2.6 log units. MRI brain and a complete skeletal survey did not show any abnormal findings. Genetic testing did not reveal any homozygous deletion of NPHP 1 gene and other genetic testing was not done. A clinical diagnosis of Senior-Loken syndrome was made and the patient was treated with dialysis and later underwent successful cadaveric kidney transplant.

Discussion

Etiology/Pathogenesis

Senior-Loken is an autosomal recessive disorder and its etiology is attributed to mutations in the known nephronophthisis (NPHP) genes. Positional cloning of nine genes (NPHP1-9) as mutated in NPHP and characterization of their coded proteins led to the concept of "ciliopathies". This theory states that the products of all mutated genes in cystic kidney diseases are expressed in primary cilia or centrosomes of renal epithelial cells. Primary cilia are sensory organelles that connect mechanosensory, visual, osmotic, and other stimuli to mechanisms of cell-cycle control and epithelial cell polarity. Thus, the ciliary theory explains the multisystem involvement of NPHP (5). Table 1 shows the genetic disorders and the clinical syndromes associated with NPHP.

Mutations in NPHP1 through 9 accounts for 50–60% of all NPHP cases (6). NPHP1 to NPHP9 mutations have been reported in cases of juvenile NPHP; mutations in NPHP2 have been found only in patients with infantile NPHP. NPHP1 mutations occurred in ~20% to 40% of NPHP cases, whereas mutations in the other genes account for a very low percentage of cases. However, with the exception of a moderate form of retinal degeneration or Joubert syndrome, most patients with NPHP1 deletions or mutations have no extra-renal symptoms.

NPHP1 was the first NPHP gene I identified. Homozygous deletions of B250 kb DNA in the region 2q13 are the most frequent genetic abnormality found, accounting for about 25% cases of NPHP (7). NPHP1 encodes a protein product named nephrocystin-1. Nephrocystin is localized at the cell–cell junction and at the cell–matrix interface, suggesting an important function in maintaining tubular epithelium (8, 9).

Mutations in NPHP2 and a now recently described NPHP3 mutation give rise to infantile NPHP (10). These mutations are rare, accounting for only 1% of all the cases of NPHP worldwide. The gene encodes the protein named inversin, which has a dynamic distribution during the cell cycle (11, 12). Infantile NPHP type 2 can be associated with retinitis pigmentosa, liver fibrosis, ataxia, and situs inversus with developmental and mental retardation. NPHP3 is located on 3q22 and encodes nephrocystin-3, which interacts with nephrocystin-1 and inversin and can inhibit canonical wnt signaling. Interestingly,

Table 1. Genetic defects associated with NPHP with clinical presentation

Gene	Protein	Locus	Clinical presentation
NPHP1	Nephrocystin 1	2q13	Mild JS, mild RP, Cogan, juvenile NPHP
NPHP2	Inversin	9q31	RP, liver fibrosis, hypertension, infantile NPHP
NPHP3	Nephrocystin 3	3q22	Liver fibrosis, RP, situs inversus, MKS, juvenile NPHP, infantile NPHP
NPHP4	Nephrocystin 4/nephroretinin	1p36	Cogan, RP, juvenile NPHP
NPHP5	Nephrocystin 5	3q21	Severe RP, juvenile NPHP
NPHP6	Nephrocystin 6/CEP290	12q21	JS, severe RP Isolated RP, JS, MKS,BBS, juvenile NPHP
NPHP7	GLIS2	16p	Juvenile NPHP
NPHP8	RPGRIP1L	17q11	JS, MKS, juvenile NPHP
NPHP9	NEK8	6q23	Juvenile and infantile NPHP

NPHP, Nephronophthisis; **JS**, Joubert syndrome; **MKS**, Meckel-Gruber syndrome.

the pcy mouse, a spontaneously occurring renal cystic disease model that closely resembles nephronophthisis, harbors a homozygous mutation in the mouse NPHP3 that most likely causes the kidney phenotype (13). Recent observations that the pcy-associated renal cystic disease is amenable to treatment with a vasopressin-2 receptor antagonist (14) are encouraging for possible future treatment for these diseases.

The NPHP4 gene located on chromosome 1p36 encodes a 1,426 amino acid protein called nephrocystin - 4 / nephroretinin that encodes nephrocystin - 4 a highly conserved protein which interacts with nephrocystin - 1 (15). Nephrocytsin - 4 complexes with α-tubulin and localizes to the primary cilium and basal bodies. Recently, nephrocystin-4 has been reported to interact with RPGRIP1L [RP guanosine riphosphatase (GTPase) regulator interacting protein] (11) which is a component of the photoreceptors that are mutated in patients with Leber's Amaurosis causing autosomal early-onset retinitis pigmentosa without kidney disease (16).

NPHP5 were reported only in patients with NPHP in combination with severe retinal degeneration and early blindness—Senior-Loken syndrome. NPHP5 encodes an IQ domain protein called nephrocystin-5 that is expressed in connecting cilia of photoreceptors where it is associated with calmodulin and retinitis pigmentosa GTPase regulator (17). NPHP6, also known as CEP290, encodes a centrosomal protein that activates ATF4, a transcription factor involved in the control of the cell cycle. Patients with mutations in NPHP5 or NPHP6 genes exhibit early onset retinitis pigmentosa.

The NPHP7/GLIS2 gene encodes the Kruppel-like zinc finger transcription factor GLIS2 that localizes to both the primary cilia and the nucleus. Retinitis Pigmentosa has been observed in association with

Table 2. Syndromes associated with NPHP and their salient features

Syndrome	Key features
Senior-Loken syndrome	Retinitis pigmentosa and NPHP
Senior-Boichis syndrome	Liver fibrosis, NPHP, tapetoretinal degeneration
Saldino-Mainzer syndrome	Bone anomalies and NPHP
Joubert syndrome	Congenital hypotonia, Ataxia, NPHP, Developmental delay, oculomotor apraxia or Abnormal breathing pattern with cerebellar vermis aplasia
COACH syndrome	Cerebellar vermis hypoplasia, Oligophrenia, Congenital Ataxia, Coloboma, and Hepatic fibrosis
Arima syndrome	Cerebellar anomalies, Retinopathy, and Polycystic kidneys
Alstrom syndrome	NPHP, Retinal dystrophy, Severe deafness, Diabetes mellitus and Obesity
Cogan syndrome	Occulomotor apraxia, NPHP
RHYNS syndrome	Retinitis pigmentosa, Hypopituitarism, NPHP, and Skeletal dysplasia
Jeune's dystrophy	Skeletal deformity, Respiratory insufficiency with Retinal dystrophy and NPHP
Meckel–Gruber syndrome	Occipital meningoencephalocoele, NPHP, cystic kidneys and postaxial polydactyly

NPHP, Nephronophthisis

mutations in most NPHP genes except NPHP7 (18).

The NPHP8/ RPGRIP1L gene encodes a protein named retinitis pigmentosa GTPase regulator interacting protein 1-like protein (RPGRIP1L). The NPHP9/NEK8 gene encodes the NEK8 protein (never in mitosis A-related kinase 8). Mutations of this gene have been described in two families with NPHP and one consanguineous family with infantile NPHP (19).

Epidemiology

The incidence of NPHP is estimated as nine patients in about 8.5 million in the United States and has been reported in all parts of the world without any special predominance (20). A recent study reported an incidence of 1 in 50,000-60,000 live births (21) but these figures may be an underestimate because of the delay in diagnosis due to the non-specific features of NPHP that may limit recognition. Senior-Loken syndrome accounts for about 10% of cases of NPHP.

Clinical features

The renal involvement in NPHP syndromes is well defined and was first described by Smith and Graham in 1945 (22) and Fanconi *et al* who introduced the term "familial juvenile nephronophthisis (23). NPHP forms a wide spectrum of multi-system diseases and is divided into infantile, juvenile, and adolescent forms based on the age of onset of renal failure. Three clinical forms of NPHP are distinguished by onset of ESKD: Infantile, juvenile, and adolescent NPHP, which manifest with ESKD at the median ages of 2, 13, and 19 years of age, respectively (24).

Polyuria, polydipsia, and impaired concentrating ability are the earliest clinical signs (25, 26). Later, progression to severe anemia, growth retardation, and ESKD occurs. Associated ocular findings include nystagmus, poor pupillary reflexes, retinal mottling,

and high myopia. Visual field testing usually shows severe annular constriction of the visual fields (1, 2, 27). Hyperchloremic acidosis with hypernatremia are the usual electrolyte abnormalities. UA is inconsistent for blood, protein or casts. A decreased urinary concentrating defect is demonstrated by a low urinary osmolarity (<400 mosm/kg in the first urine sample in the morning), which does not increase after desmopressin acetate administration (28). Renal failure is often present at the time of presentation. ESKD develops at a mean age of about 13 years but can also occur in some rare cases much later during adulthood (29). Late-onset renal failure in a context of kidney changes typical of nephronophthisis should raise the suspicion of a diagnosis of medullary cystic disease (MCD), a rare disorder once confused with NPHP under the term NPHP-MCD complex, but now clearly distinguished from NPHP, both clinically and genetically (30-32).

Kidney ultrasound may show increased echogenicity with renal cysts in the corticomedullary junction. However, the lack of cysts does not exclude NPHP (33). Histologically the disease is characterized by interstitial fibrosis, tubular atrophy with corticomedullary cyst development, and disruption of the tubular basement membrane (34, 35). The adolescent form has been associated with NPHP3 gene at a mean age of 19 years. NPHP shares pathogenic features with other cystic kidney diseases but differs in that kidney enlargement is absent and fibrosis predominates.

There are several extra-renal manifestations of NPHP. Most commonly the eye is involved, in about one third of cases in the form of tapeto-retinal degeneration, Leber's congenital amaurosis, punctuate albescence retinopathy, and retinitis pigmentosa. Based on the duration of retinal involvement, SLS is divided into early-onset SLS which includes Leber's congenital amaurosis and blindness at birth, and late-onset SLS which manifests as vision problems at night with subsequent progression (3). Retinal degeneration is characterized by complete extinction of the electroretinogram which precedes the development of visual and fundoscopic signs of retinitis pigmentosa. Other extra-renal manifestations are seen in 10-20 % cases of NPHP and involve brain, liver, and skeletal anomalies.

Our patient displayed typical retinal changes of SLS on ophthalmologic exam and electroretinography. She also had absent pupillary reflexes although congenital nystagmus was not described. She presented with ESKD and echogenic large kidneys on ultrasound. The medullary cysts characteristic on NPHP were not observed on ultrasound of her kidneys but, as previously noted; cysts may not be present in all cases of NPHP (33). Limited genetic analysis was conducted on our patient and only NPHP1 was excluded. Her overall clinical picture is certainly consistent with SLS.

Associated renal-retinal syndromes

Senior-Loken syndrome has several overlaps and associations with Senior-Boichis syndrome (liver fibrosis, NPHP, tapetoretinal degeneration), Saldino-Mainzer syndrome with bone anomalies, Joubert syndrome (congenital hypotonia, ataxia, developmental delay and either oculomotor apraxia or abnormal breathing pattern with cerebellar vermis aplasia), COACH syndrome (Cerebellar vermis hypoplasia, Oligophrenia, congenital Ataxia, Coloboma, and Hepatic fibrosis), Arima syndrome (cerebellar anomalies, retinopathy, and polycystic kidneys), Alstrom syndrome (NPHP, retinal dystrophy, severe deafness, diabetes mellitus and obesity), RHYNS syndrome (retinitis pigmentosa, hypopituitarism, NPHP, and skeletal dysplasia) and Jeune's dystrophy (skeletal deformity, respiratory insufficiency with retinal dystrophy and NPHP) (36). Table 2 outlines these syndromes and their associated clinical presentations.

Joubert syndrome

Joubert syndrome is a multi-organ disorder

consisting of congenital hypotonia, ataxia, developmental delay and either oculomotor apraxia or abnormal breathing pattern with cerebellar vermis aplasia (37). The incidence is reported as 1 in 100,000. The etiology of Joubert syndrome is attributed to three different genes, NPHP1, AHI and NPHP6. Recently, JBTS1 on chromosome 9q34.3 and JBTS2/CORS2 on chromosome 11p12-q13.3 have been identified as additional loci. (38). AH1 accounts for about 20% of the cases of Joubert syndrome. Brain imaging reveals a characteristic molar tooth sign in the cerebellum (39). Joubert syndrome is classified into two groups, those with retinal dystrophy and those without retinal dystrophy. In this classification, renal disease is present only in the group with retinal involvement (type B) (40). Retinal disease consists of a pigmentary retinopathy that may be indistinguishable from classic retinitis pigmentosa. It can occasionally be severe with neonatal onset of congenital blindness and an attenuated or extinguished electroretinogram (ERG) that resembles Leber congenital amaurosis. However, the retinal disease may not be progressive and is not always present in infancy or early childhood. Many children with Joubert syndrome demonstrate horizontal nystagmus at birth which improves with age. Torsional and pendular rotatory nystagmuses have also been observed (41).

Meckel-Gruber syndrome

Meckel-Gruber syndrome (MKS) is an autosomal recessive disorder characterized by anomalies of the central nervous system resulting in mental retardation, cystic dysplasia of the kidneys, and malformations of the hands and feet. The first detailed description of the syndrome is attributed Johann Friedrich Meckel in 1822 (42). The incidence of MKS varies from 1 in 13 250 to 1 in 140 000 live births. Interestingly, mutations in the NPHP6, NPHP8, and MKS3 genes have been found in patients with MKS as well as in patients with Joubert syndrome, suggesting that these two conditions represent a broad spectrum of the same underlying disorder (43-45). Cystic renal disease is the most common manifestation. Radiologically, the kidneys in MKS may resemble recessive polycystic kidney disease but in MKS the cysts are small (1–2 mm), involve mainly the collecting ducts, and are radially oriented (46).

COACH syndrome

COACH syndrome is one of the associated syndromes of NPHP. It is an extremely rare disorder with hypoplasia of the cerebellar vermis, oligophrenia, congenital ataxia, coloboma and hepatic fibrosis. Verloes and Lambotte were the first to describe this syndrome (47). Most cases of COACH syndrome include dysplastic renal disease such as fibrocystic renal disease, atrophic tubules, and tubular basement membrane thickening (48). Foell *et al* showed that 70% with COACH syndrome have renal abnormalities, and, unlike most of the other NPHP syndromes, it may clinically manifest only in adulthood (49).

Arima syndrome

Arima syndrome is an autosomal recessive disorder characterized by agenesis of the cerebellar vermis, ocular abnormalities, cystic kidney disease, and, in some cases, liver disease. It shares phenotypic features with Joubert syndrome, COACH syndrome and familial juvenile nephronophthisis (50). Matsuzaka *et al* in 1986 reported 3 unrelated patients, 2 boys and a girl, with severe visual impairment from early infancy, psychomotor retardation, hypotonia, nystagmus, blepharoptosis, and progressive chronic kidney disease. Postmortem examination of the 2 boys, who died at ages 12 and 13 years, showed almost total aplasia of the cerebellar vermis, malformations of the brainstem, including pachygyria of the inferior olivary nuclei and partial absence and anomalous position of the pyramidal tracts, and polycystic kidneys. One patient had hepatic steatosis and the other had hepatic fibrosis. Matsuzaka *et al* concluded

that the constellation of findings was consistent with a distinct clinicopathologic entity, which they termed cerebro-oculo-hepato-renal syndrome or "Arima syndrome" (51).

Alstrom syndrome

Alstrom syndrome is characterized by a progressive loss of vision and hearing, a form of heart disease that enlarges and weakens the heart muscle (dilated cardiomyopathy), obesity, type 2 diabetes mellitus, and short stature (52). This disorder can also cause serious or life-threatening medical problems involving liver, kidneys, bladder, and lungs. Mutations in the ALMS1 gene cause Alstrom syndrome (53). Mutations in this gene probably lead to the production of an abnormally short, nonfunctional version of the ALMS1 protein. This protein is normally present at low levels in most tissues, so a loss of the protein's normal function may help explain why the signs and symptoms of Alstrom syndrome affect many parts of the body. The retinal dystrophy in Alstrom syndrome usually develops within a few weeks after birth. The first symptoms are nystagmus and extreme light sensitivity and almost all children have poor vision in the first year of life (54). Patients may have symptoms ranging from chronic mild kidney dysfunction to end-stage kidney disease. Biopsy may reveal hyalinization of tubules and interstitial fibrosis (55).

RHYNS syndrome

Rhyns syndrome is a combination of retinitis pigmentosa, hypopituitarism, NPHP, and skeletal dysplasia. It was first described by Di Rocco *et al* in 1997 (56). Nephronophthisis was suggested as one of the cardinal features of RHYNS syndrome. Several syndromes overlap with RHYNS syndrome and need to be considered in the differential diagnosis. The association of retinitis pigmentosa with early peripheral visual loss, hypopitutarism, and acromegalic skeletal dysplasia with or without renal medullary cystic disease is unique and distinctive from other conditions associated with retinitis pigmentosa, such as Senior-Loken syndrome, Mainzer-Saldino syndrome, Bardet-Biedl syndrome, and Alstrom syndrome (57).

Conclusions

The concept of "retinal ciliopathies" brings to attention the importance of molecular analysis in the diagnosis and understanding of this organelle as well as providing a potential common target for therapies for these disorders. Identification of patients with such syndromes ensures advancement in genetic mapping exclusion and chromosomal localization of the genetic defect. Although our patient lacked some of the classical findings of SLS and incomplete genetic analysis precludes definitive diagnosis, her clinical presentation is consistent with SLS. The treatment of choice for NPHP is currently kidney transplantation when ESKD is reached as recurrence of the disease is rare. The recent observation that the pcy-associated renal cystic disease is amenable to treatment with a vasopressin-2 receptor antagonist opens new perspectives for potential therapeutic strategies for NPHP. Although these disorders are relatively rare, infants and children with such visual disturbances should at least have kidney function evaluated and, if abnormalities are discovered, undergo kidney imaging. Since these syndromes may occasionally present in young adults, adult nephrologists should consider NPHP in the differential diagnosis of ESKD in a patient with retinal disease. Once NPHP is suspected, patients need regular monitoring of kidney and liver function, renal ultrasound, eye examinations, and brain imaging to rule out cerebral malformations and to prepare for kidney transplantation.

Conflict of interest

None declared.

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