Case Report

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Clinical features of Senior–Loken syndrome with IQCB1/NPHP5 mutation in a Filipino man

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The Senior–Loken syndrome was first described in 1961 as an oculo-renal disease consisting of familial juvenile nephronophthisis and Leber congenital amaurosis. It is a rare autosomal recessive disorder with a prevalence of 1:1,000,000 caused by mutations in nine genes (NPHP 1-8 and NPHP 10). Ocular manifestations (e.g., photophobia, nystagmus, and extreme hyperopia) occur within the first few years of life while renal manifestations (e.g., formation of multiple cysts impairing kidney function and end-stage renal disease) appear in late childhood to adolescence. Here, we report a case of a Filipino male presenting with rotatory nystagmus and progressive deterioration of vision since childhood. He had congenital amaurosis and juvenile nephronophthisis that progressed to end stage renal disease by age 19. All laboratory and imaging findings were consistent with chronic kidney disease. Molecular genetic testing of ciliopathy-related genes was performed revealing a homozygous mutation in exon 11 of the IQCB1/NPHP5 gene, c.1090C>T (p.Arg364*). This sequence change created a premature translational stop signal resulting in a truncated protein product, nephrocystin-5 and its consequent loss of function. His symptoms eventually improved with initiation dialysis. The prognosis of Senior–Loken syndrome remains dismal and a high index of suspicion, early diagnosis and timely intervention of renal complications are warranted.

Key words: Ciliopathies, IQCB1 protein, human, Leber congenital amaurosis, Nephronophthisis, familial juvenil, Senior Loken syndrome.

Introduction

The Senior–Loken syndrome (SLSN) was first concurrently described by Senior et al. [1] and Loken et al. [2] in 1961 as a combination of familial juvenile nephronophthisis and Leber congenital amaurosis. It is a rare autosomal recessive oculo-renal disease with a prevalence of 1:1,000,000 [3,4] belonging to the group of rare diseases called nephronophthisis (NPHP, OMIM 2561000). Presently, mutations in nine genes (NPHP 1-8 and NPHP 10) have been observed in patients with SLS [4]. IQCB1/NPHP5 mutations are the major cause of the SLSN type 5 (SLSN5, OMIM 609254) presenting as the classic features of retinopathy and end stage renal disease. Here, we report a case of SLSN in a Filipino man with the IQCB1/NPHP5 mutation. To date, there have been no on SLSN from Filipino patients.

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Case

A 19-year old male was admitted at our emergency room for intractable vomiting, dysgeusia, epigastric pain, and generalized weakness. He was the eldest of three siblings born to a healthy non-consanguineous couple of Filipino descent (Fig. 1). Both parents and two older sisters were completely asymptomatic. He had persistent rotatory nystagmus and progressive deterioration of vision since childhood, with current visual acuity of light perception for both eyes. He attended special education until the second grade, and subsequently entered the regular education system but still requiring assistance in schoolwork from his parents. Important physical examination findings include the following: elevated blood pressure of 140-150 mmHg systolic and 90-100 mmHg diastolic, body weight less than 3rd percentile for age, persistent rotatory nystagmus of both eyes, and pale palpebral conjunctivae.

Relevant laboratory findings on admission showed a serum creatinine level of 1,195 μmol/L, blood urea nitrogen level of 28.57 mmol/L, serum sodium of 106 mmol/L, serum potassium of 5.6 mmol/L and normocytic, normochromic anaemia (haemoglobin of 66 g/L). Imaging of the kidneys using computed tomography revealed bilaterally small kidneys consistent with renal parenchymal disease, and two fairly defined hypodensities on the left kidney. Fundoscopy of both eyes revealed pale optic discs, attenuated blood vessels and diffuse bony spicules compatible with Leber congenital amaurosis. The glaring ophthalmologic symptoms (persistent nystagmus and light perception on visual acuity) since childhood as well as the fundoscopic findings of diffuse retinal atrophy led our team to suspect an oculo-renal genetic syndrome, of which the most consistent would be a nephronophthisis. Buccal DNA was extracted, and sequence analysis and deletion/duplication testing of the 102 genes (Invitae Ciliopathies Panel) was performed revealing a homozygous mutation in the IQCB1 gene (Table 1) consistent with SLSN5. This sequence change creates a premature translational stop signal (p.Arg364*) in the IQCB1 gene therefore, resulting in either an absent or truncated protein product of nephrocystin-5 and hence, its consequent pathogenic loss of function [3].

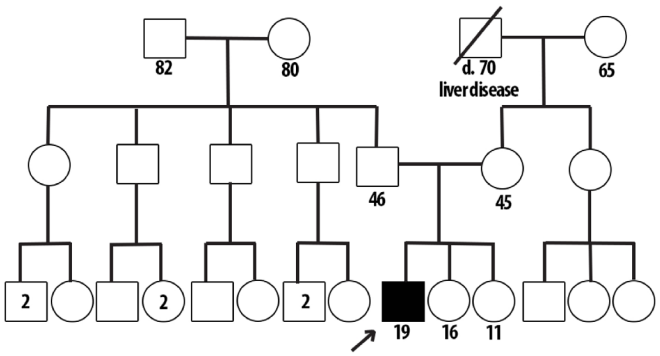

Fig. 1. The three-generation pedigree of the patient.

Our patient underwent haemodialysis and blood transfusion with gradual improvement of his condition. However, visual symptoms did not improve. He was successfully discharged after one week of admission and is currently on regular follow-up with our outpatient service where post-genetic testing counselling was rendered to both the patient and his parents. During this follow-up, he was seen ambulatory with an improved overall well-being.

Discussion

The SLSN5 caused by mutations in the NPHP5/ICQB1 gene was first identified by Otto et al. [3] in 2005. The NPHP5/ICQB1 gene, codes for a protein, nephronocystin-5, also known as the IQ calmodulin-binding motif-containing protein 1. The mutation leads to the formation of a truncated version of nephrocystin-5, which interacts directly with calmodulin and forms a complex with retinitis pigmentosa GTPase regulator (RPGR). Both nephrocystin and RPGR are localized in the ciliary apparatus of photoreceptor cells in the retina and renal epithelial cells, providing a basis for the oculo-renal syndrome observed when NPHP5 is mutated [4]. Patients with SLSN5 invariably develop early-onset retinitis pigmentosa and atrophy, with variable onset of renal manifestations, eventually leading to end stage renal disease from the first to third decade [4].

While not yet reported in the Philippines, SLSN5 has been reported in various Asian populations [5-12]. Notably, in the two studies of siblings, of Chinese [9] and Kuwaiti [10] descent, respectively, both presented with many similar characteristics

Table 1. Genetic testing results of the patient

Gene	Variant	Zygosity	Classification
IQCB1	c.1090C>T (p.Arg364*)	Homozygous	Pathogenic
CCDC65	c.930A>T (p.Gln310His)	Heterozygous	Uncertain significance
WDR34	c.1565G>A (p.Arg522Gln)	Heterozygous	Uncertain significance

Table 2. Summary of clinical characteristics of reported cases of Senior–Loken syndrome in patients of Asian descent

Report	Age (yr) /sex	Ethnicity	Manifestations	Consanguinity
Clarke et al. [5]	Sibling A: 10/F	Indian	Leber congenital amaurosis Mild to moderate sensorineural hearing loss	(+)
	Sibling B: 8/M		End-stage renal disease	
AlFadhel and AlAmir [6]	11/F	Arabic	Retinitis pigmentosa End-stage renal disease	(+)
Haghighi et al. [7]	26/M	Iranian	Retinitis pigmentosa End-stage renal disease	(+)
Aggarwal et al. [8]	19/M	Indian	Retinitis pigmentosa End-stage renal disease Madarosis Small hands	(–)
Tong et al. [9]	Sibling A: 16/F	Chinese	Leber congenital amaurosis	(–)
	Sibling B: 12/F		End-stage renal disease	
Marafie and Mulla [10]	Sibling A: 18/F	Kuwait	Leber congenital amaurosis End-stage renal failure	(+)
	Sibling B: 9/M		Leber congenital amaurosis End-stage renal failure	
Kaur et al. [11]	9/F	Indian	Retinitis pigmentosa End-stage renal disease	(–)
Khairil-Ridzwan et al. [12]	14/M	Chinese	Coat's disease End-stage renal disease	(–)
Index patient	19/M	Filipino	Leber congenital amaurosis End-stage renal failure	(–)

F, female; M, male.

to our patient: Leber congenital amaurosis, growth retardation, anemia, polycystic kidney disease, and development of end-stage renal disease in the second decade of life. Different mutations in the same gene have also been observed in Indian [5], Arabian [6], Iranian [8], and Chinese [9] families, notably from consanguineous lineages, which showed a highly variable onset of retinitis pigmentosa (ranging from birth to teenage years) with end-stage renal disease developing from the first to the second decade (Table 2) [5-12].

The pathogenesis of SLSN can be explained by the ciliary theory of polycystic kidney diseases. A mutation in a single NPHP gene is enough to cause the syndrome, indicating that their protein products are necessary for renal function. NPHP1 and NPHP2/inversion were the first genes to be localized in the primary cilia of renal epithelial cells [13], and resulting mutations in various components of cilia, basal bodies, and centrosomes have been shown to cause cystic kidney diseases. SLSN demonstrates that these highly-conserved proteins play a vital role in the functioning of cilia in other parts of the body notably the sensory system. Ciliated receptors process a variety of stimuli, including photosensation, mechanosensation, osmosensation, and olfactory sensation, hence the pathogenesis of these mutations stems from the inability of cilia to receive or process these cues [14].

The prognosis of SLSN primarily depends on early diagnosis and a high index of suspicion, it should be included in the differential diagnoses for young patients presenting with visual decline and progressive renal failure; and timely management of the renal complications, which is the major cause of mortality. However, there are currently no available treatment options to prevent progression of visual loss.

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