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Co-Occurrence of Nephronophthisis Type 1 and Alström Syndrome: A Case Report

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Abstract
We describe the unique case of a patient in whom two ciliopathies with autosomal recessive transmission were clinically and molecularly diagnosed: nephronophthisis type 1 (*NPHP1*) and Alström syndrome (AS). *NPHP1* is one of the main genetic causes of terminal kidney failure in childhood. AS is an ultra-rare multi-systemic disease, characterized by progressive kidney disease, hepatic failure, dystrophy of the rods and cones to blindness, slowly progressive neurosensory deafness, dilated cardiomyopathy, obesity, insulin resistance/type 2 diabetes mellitus. The coexistence in the same patient of two rare syndromes with overlapping clinical manifestations but genetically different is an eventuality to be considered. This case report would describe the onset and progression of the multi-organ manifestations of both syndromes to highlight that ciliopathies present a strong phenotype overlap but also specific peculiarities. Therefore, to make a correct diagnosis that is essential to achieve the best clinical management could be challenging.

Background

Ciliopathies are a large group of genetically inherited diseases characterized by non-motile cilia dysfunction [1]. Cilia, localized on the apical portion of eukaryotic cells, play a crucial role in regulating cell proliferation and differentiation, tissue morphogenesis, and intracellular signal transduction [1].

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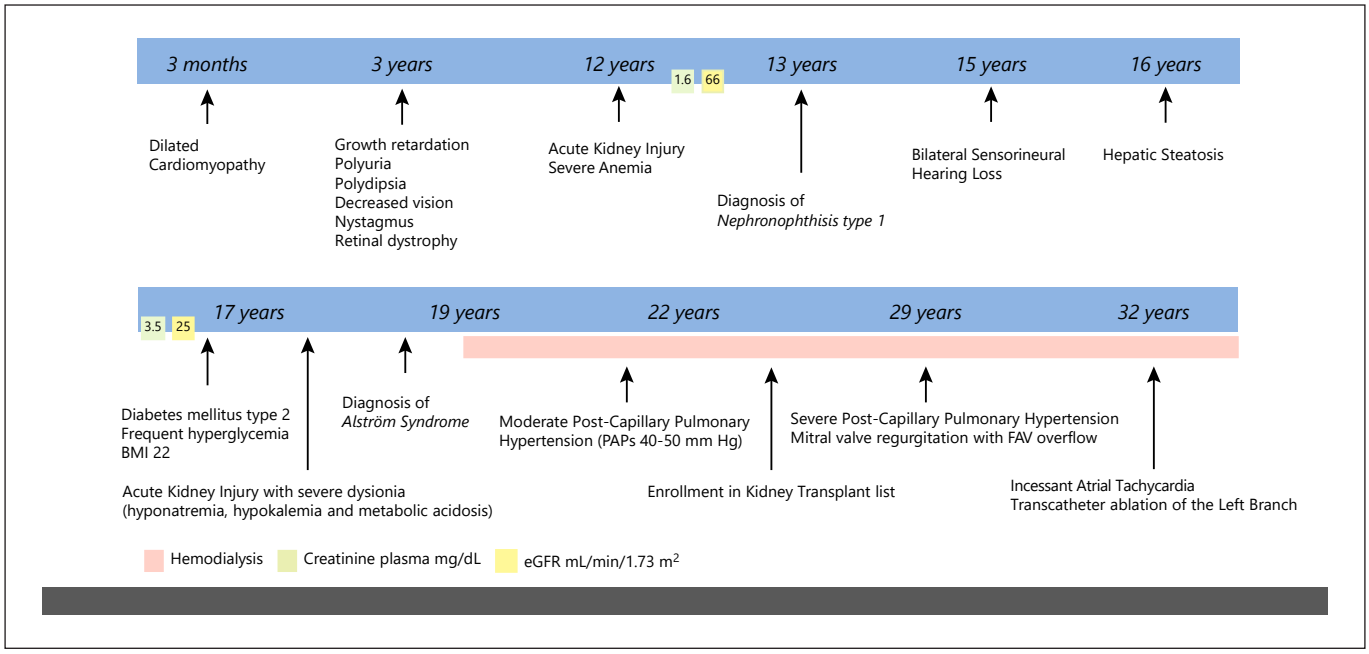

Fig. 1. Timeline of the main clinical events, diagnostic examinations, and biochemical data in our patient.

Up to now, the literature describes more than 35 ciliopathies associated with a huge and progressively increasing number of mutations in more than 180 genes involved in the genesis of primary cilia [1]. Ciliopathies present a wide spectrum of different phenotypes, from adult onset single organ involvement to multiple congenital malformations. Renal ciliopathies are represented by cystic kidney disease (autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease), Meckel-Gruber syndrome, Bardet-Biedl syndrome, and nephronophthisis. Other organs typically involved in these etiopathogenic entities are eyes (retinitis pigmentosa; Senior-Løken syndrome), liver fibrosis (Caroli disease), and malformation of the central nervous system (Joubert syndrome) [2].

The most frequent renal ciliopathy is nephronophthisis. The type 1 or juvenile nephronophthisis (*NPHP1*) is a genetic recessive disease due to mutations/and or deletion of the *NPHP1* gene mapped on chromosome 2q13. *NPHP1* may lead to end-stage kidney disease (ESKD) in 5–10% of cases during childhood or adolescence [2]. *NPHP1* frequently presents as an isolated renal phenotype, but also extra-renal manifestations are described such as progressive retinal dystrophy (Senior-Løken syndrome) [3, 4], neurological abnormalities leading to cerebellar ocular-renal syndrome (Joubert syndrome), and liver fibrosis [5, 6].

Alström syndrome (AS) is an ultra-rare multisystem monogenic recessive disorder caused by mutation in *ALMS1* gene, located on chromosome 2p13 [7]. The clinical presentation of AS resembles nephronophthisis, with progressive kidney dysfunction, eyes involvement (cone-rods dystrophy), and liver fibrosis [8], but also with sensorineural deafness, dilated cardiomyopathy (CMD), obesity, and type 2-diabetes [9]. We here described the case of a patient presenting overlapping clinical phenotypes of these two ciliopathies and the relative molecular characterization.

Case Presentation

A 13-year-old Caucasian male was admitted at our hospital due to onset of kidney disease with severe anemia (Hb 7.3 g/dL; n.l. 12.5–17.5 g/dL) and reduced kidney function with a serum creatinine of 1.6 mg/dL (n.l.< 0.9 mg/dL) and an estimated glomerular filtration rate of 66 mL/min/1.73 m^2 (n.l.> 120 mL/min/1.73 m^2). Ultrasonography showed small kidneys, multiple cysts, and loss of cortico-medullary differentiation; the cerebral MRI was reported as negative. Ophthalmological (electroretinogram and fundus oculi) showed retinal dystrophy and progressive night blindness.

He was the third-born baby from healthy non-consanguineous parents. During the first year of life, he showed growing retardation due to food refusal and vomiting. Polyuria and polydipsia, progressive decrease in virus and nystagmus with a moderate dilated CMD treated with furosemide and ACE inhibitors characterized the first years of life (see Fig. 1).

Considering the above-reported data, we supposed a nephronophthisis, confirmed by the single tagged site analysis that identified a homozygous deletion of the *NPHP1* gene (NM_000272: [*NPHP1*-del]) (OMIM #256100; ClinVar VCV000003511.1) as already described [5, 10]. At 15 and 16 years old, the patient developed mild sensorineural deafness and hepatic steatosis, respectively. At the age of 17, he presented type 2 diabetes mellitus (DM). Considering the progressive deafness and the type 2 DM, we hypothesized a possible coexistence of nephronophthisis and AS.

At that time, the AS causative gene (*ALMS1*) had just been described and we identified a homozygous variant on exon 8 (NM_015120:c.2176dup [p.Tyr726Leu*fs**12]) (OMIM #203800; ClinVar VCV000555437.10) by Sanger sequencing [11]. Therefore, we concluded the molecular diagnosis with the association of two recessive diseases.

The patient presented a progressive decrease of kidney function up to ESKD at 19 years old, and he started chronic hemodialysis. Despite ESKD, our patient conserved a diuresis of 2–3 L/die.

Mild-to-moderate pulmonary hypertension (PAPs 40–50 mm Hg) was observed during the investigations for the enrolment in deceased kidney donor waiting list, when the patient was 29 years old. In the following years, pulmonary hypertension worsened, so that β-blocker and amiodarone were further added to therapy, and at the age of 32, the patient developed incessant atrial tachycardia due to a minor left bundle branch disturbance. Therefore, transcatheter ablation of the left bundle branch was performed with subsequent good heart rate control [12].

Considering the complexity of the cardiac phenotype, the worsening of his clinical condition, and the availability of the new sequencing technologies, we performed a clinical exome by next-generation sequencing [13] of the trio that confirmed the coexistence of *NPHP1* homozygous deletion and the pathogenic homozygous variant in *ALMS1*. No other significant variants were identified in other ciliopathy and CMD-associated genes. Segregation analysis confirmed the heterozygous state for the two molecular defects in both parents. Currently, our patient continues hemodialytic treatment three times weekly while waiting for kidney transplant and maintains preserved diuresis.

Discussion

In this report, we describe the peculiar coexistence of two autosomal recessive ciliopathies in the same individual. Ciliopathies are a genetically heterogeneous group of diseases with autosomal dominant, recessive, and oligogenic inheritance. They present similar phenotypes varying from cystic kidney disease, neurological phenotype, liver fibrosis, blindness, diabetes, and obesity caused by several different gene products composing or influencing the primary cilia [1].

Nephronophthisis is a group of ciliopathy presenting a major renal involvement; up to date, 25 genes have been discovered as causative of the disease [6]. *NPHP1* is the most common gene involved leading usually to ESKD within the first two decades of life. Extra-renal manifestations of *NPHP1* are shared with many other ciliopathies, such as cerebellar malformations, nystagmus, and intellectual disability (typical of Joubert's syndrome), retinal degeneration (typical of Senior-Løken syndrome or Cogan's syndrome), and impairment of the liver [4, 5].

Several of these features are common findings in nephronophthisis, such as ocular and kidney phenotypes, but deafness, obesity, and CMD are peculiar of AS [7, 8, 11, 14]. We are presenting the case of a patient who developed different phenotypes over time. The clinical history is filled with the occurrence of signs and symptoms related to the two syndromes.

As far as extra-renal manifestations are concerned, our patient presents delayed psychomotor development, liver fibrosis, and brain malformations as expected in *NPHP1* [6]. On the other hand, he developed retinitis pigmentosa, bilateral sensorineural deafness, type 2 DM, dilated CMD, and scoliosis as expected in AS [8].

No curative therapies are currently available for both of these syndromes. The cornerstone of the clinical management is to offer promptly supportive therapies and to slow down the progression of kidney disease. Oral drugs and insulin are used to treat diabetes, hypolipidemic therapy to reduce circulating cholesterol levels and hypertriglyceridemia, hearing aids to treat cochlear dysfunction. ACE inhibitors, β-blockers, spironolactone, and transcatheter ablation could be used to counteract cardiac dysfunction. Renin-angiotensin-aldosterone system inhibitors help slow down CKD progression to ESKD. Data from the literature suggest that the major risk factors for mortality are ESKD and cardiac failure. Liver dysfunction may also influence the prognosis [6].

Both the syndromes do not recur after transplantation; thus, kidney transplant is the replacement therapy of choice. In conclusion, our report emphasizes that the clinical management of ciliopathies is challenging for pediatric nephrologist, since characterized by a wide spectrum of organs involved, severe complications, and absence of specific therapies. Moreover, all these diseases present a strong phenotype overlap making difficult a correct diagnosis that only genetic analysis can solve, as highlighted by this patient.

We identified two pathological variants in homozygosis in two different genes (*NPHP1* and *ALMS1*) in a subject with no consanguineous parents. However, the parents come from an Italian island region largely isolated from the rest of the country in previous centuries with a previously

well-recognized population isolates, correlating specific genetic variants to specific phenotypes (founder effect) [15]. Therefore, we may speculate a similar phenomenon for the two variants here reported. The increasing use of massive parallel sequencing techniques in genetic analysis together with an accurate clinical data collection could be useful to obtain early and exact diagnosis in order to provide the best clinical support to slowing the progression of CKD.

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Statement of Ethics

Ethic approval was not required by the Regional Ethic Committee (CER Liguria). All methods were performed in accordance with relevant guidelines/regulations and in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

All the authors declared no competing interests.

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Author Contributions

Lisa Rossoni, Gianluca Caridi, Andrea Angeletti, and Edoardo La Porta conceived the paper and collected the data. Lisa Rossoni, Francesca Lugani, Andrea Angeletti, Gianluca Caridi, and Edoardo La Porta analyzed the data and prepared the manuscript. Lisa Rossoni, Francesca Lugani, Silvia M. Orsi, GianMarco Ghiggeri, Andrea Angeletti, Enrico Verrina, Gianluca Caridi, and Edoardo La Porta reviewed and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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