Case Report

J Ped. Nephrology 2014;2(1):46-49
http://journals.sbmu.ac.ir/jpn

A case of Non-compaction of Left Ventricle Coexistent with Juvenile Nephronophthisis. Is this Another Presentation of Ciliopathy?

How to Cite This Article: Momtaz HE, Tanasan A, Afkhami M. A case of Non-compaction of Left Ventricle Coexistent with Juvenile Nephronophthisis. Is this Another Presentation of Ciliopathy? J Ped Nephrology 2014;2(1):46-49.

Hossein Emad Momtaz,[1]*
AsadolahTanasan,[1]
Mojdeh Afkhami[1]

1 Department of Paediatrics, Faculty of Medicine , Hamadan University of Medical Sciences, Hamadan, Iran

***Corresponding Author**
Hossein Emad Momtaz MD, Department of Paediatrics, Faculty of Medicine , Hamadan University of Medical Sciences, Hamadan, Iran

Nephronophthisis is a chronic tubulo-interstitial nephritis which can progress to end-stage renal disease. Juvenile nephronophthisis is the most common type of nephronophthisis, which accounts for 5-10% of the cases of pediatric end stage renal diseases. Left ventricular non-compaction (LVNC), a rare form of cardiomyopathy, is the result of intrauterine arrest of compaction of the endomyocardial morphogenesis. Clinical manifestations of LVNC range from asymptomatic child to a progressive deterioration in the cardiac function, congestive heart failure, arrhythmias, systemic thromboembolism and sudden cardiac death. This report presents a case of juvenile nephronophthisis with LVNC. A 15-year-old boy was referred to our nephrology outpatient clinic with a 6-month history of non-specific complaints such as lethargy, anorexia, polydipsia, polyuria, and pallor. Abdominal sonography showed a generalized increase in the parenchymal echo of kidneys. Renal biopsy was performed for him which showed nephronophthisis. Echocardiography was done and revealed LVNC. He was discharged with training for careful follow-up. Our reported case had nephronophthisis and LVNC. To the best of our knowledge, there is no report of this combination in the literature. This suggests that LVNC may be another presentation of cilia involvement. The clinical coexistence of LVNC and nephronophthisis could guide us to better localize and discover the underlying genetic mutations and the role of ciliopathies in various human diseases; Therefore, further research with a special focus on potential common derangement of cilia and protein products in these diseases is recommended.

Keywords: Juvenile nephronophthisis; Isolated Noncompaction of the Ventricular Myocardium; Ciliary Motility Disorders

Received: Nov-2013
Revised: Dec-2013
Accepted: Dec-2013

Running Title: Juvenile nephronophthisis with Non compaction of left ventricle

Introduction

Nephronophthisis (NPH), an autosomal recessive disorder initially described in 1945 by smith and graham and in 1951 by fancony, is a chronic tubulo-interstitial nephritis which can progress to end-stage renal disease (ESRD) in children [1,2]. With regard to the age of onset for ESRD, three main clinical forms of nephronophthisis have been described:

Infantile nephronophthisis, Juvenile nephronophthisis and Adolescent nephronophthisis [3]. Of these, Juvenile nephronophthisis is the most common, which accounts for 5-10% of cases of Pediatric ESRD [1]. Juvenile form of NPH affects girls and boy equally [4]. The first symptoms usually develop around 4-6 years of age. Polyuria and polydipsia related to a reduced urinary concentrating ability and loss of sodium conservation occurs early in the course of

disease, whereas glomerular filtration rate (GFR) remains in normal range [2]. Late symptoms are related to the progressive renal insufficiency and include metabolic acidosis, nausea, anorexia, anemia and weakness. ESRD develops at a mean age of about 13 years but can also occur in some rare cases much later during adulthood [4]. In approximately 10% of patients, NPHP can be associated with retinitis pigmentosa (Senior-Løken syndrome), cerebellar vermis aplasia (Joubert syndrome) and liver fibrosis [2]. NPH has recessive mutations in six different genes as causing NPHP: NPHP1, NPHP2, NPHP3, NPHP4, NPHP5, and NPHP6. Homozygous deletions in the NPHP1 gene account for approximately 25% of all NPHP cases, whereas the other genes contribute <2% each. As expected in a recessive disease, penetrance of the renal phenotype seems to be 100% [2]. Left ventricular non-compaction is a rare form of cardiomyopathy believed to be the result of intrauterine arrest of compaction of the endomyocardial morphogenesis, leading to persistence of the embryonic myocardium. On the basis of echocardiographic studies, the prevalence of disease has been estimated at 0.05% in the general population [7]. Clinical manifestations are highly variable, ranging from no symptoms to a progressive deterioration in cardiac function that results in congestive heart failure, systemic thromboembolism, arrhythmias, and sudden cardiac death [5,6]. Non compaction cardiomyopathy was first identified as an isolated condition in 1984 by Engberding and Benber [8]. Occasionally, the affected myocardial segments are hypokinetic. Non compaction of ventricle is diagnosed when the trabeculations are more than twice the thickness of the underlying ventricular wall .In these cases, the evidence of the direct blood flow from the ventricular cavity into deep intertrabecular recesses via color Doppler echocardiography analysis is helpful [8]. The disease is recently included in the 2006 classification of cardiomyopathies as a Genetic Cardiomyopathy [4]. Mutations in LDB3 (also known as "Cypher/ZASP") have been described in patients with the condition [7]. The cilium is hair-like structure that extends from the cell surface in to the extra-cellular surface. Virtually all vertebrate cell type can produce cilia. 'Ciliopathies' are an emerging class of genetic multisystemic human disorders that are caused by a multitude of largely unrelated genes that affect ciliary structure and function[3]. They are unified by shared clinical features, such as mental retardation, cystic kidney, retinal defects and polydactyly. Ciliopathies are mostly inherited as simple recessive traits, but phenotypic expressivity is under the control of numerous genetic modifires [7]. Mutations in NPHP genes cause defects in signaling mechanisms that involve the signaling pathway, resulting in defects of planar cell polarity and tissue maintenance.in the patient with mutation of NPHP2, ventricular septal defect as a congenital cardiac malformation was reporte [9]. To best of our knowledge this is the first report of association between nephronophthisis and non-compaction of left ventricle in the literature. although this may only be a coincidence but some evidences from other few reports make us to suggest that non compaction of left ventricle may be another presentation of ciliary dysfunction. Further researches are needed to confirm this possibility.

Case Report

A 15-year-old boy was referred to our nephrology outpatient clinic with a 6-month history of non-specific complaints such as lethargy, anorexia, polydipsia, polyuria, and pallor. Past medical history was unremarkable for hematuria, urinary tract infection, and urologic problems such as PUVD or neurogenic bladder. Also, he had no history of cardiac involvement such as dyspnea, orthopnea, and palpitation. The drug history was negative for any known nephrotoxic agent. The family history was negative for renal or cardiac involvement. When he was visited first, his blood pressure was 110/70 (below 95 percentile) with regular pulse beats of 95 beats/min. His physical examination only showed pallor and his weight and height were 40kg and 156 cm (BMI=16.5). Laboratory tests revealed elevated levels of BUN and Creatinine (BUN=40mg/dl, Creatinine=3.1mg/dl) and anemia (Hb=8.9 g/dl). LFT and other electrolytes were normal (AST=25, ALT=38, Na=136, K=4.2, Ca=8/1). Urinalysis was negative for protein and blood, and only showed hyposthenuria (Specific gravity = 1.008). ECG and chest X-ray had no significant findings. On abdominal ultrasound, both kidneys were normal in size but with a generalized increase in parenchymal echogenicity. A simple cyst (15*20 mm) was reported in the lower lobe of the left kidney. Echocardiography was done and revealed non-compaction of the left ventricle (Fig 1). Renal biopsy was done for him and showed interstitial

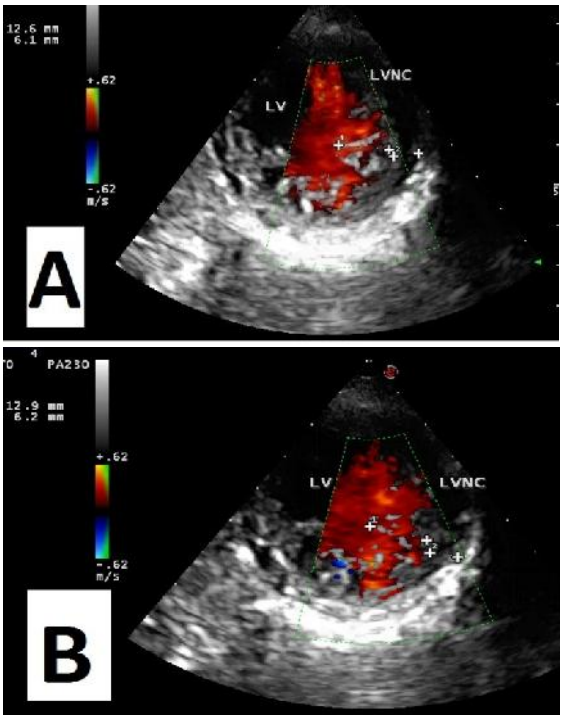

Fig 1 Non compaction of the left ventricle A,B

fibrosis, mild focal chronic interstitial inflammation, tubular atrophy and thickening and lamellation of the tubular basement membrane, consistent with nephronophthisis (Fig 2). He was discharged with training for careful follow-up.

Discussion

Cilia are filiform microtubular structures, anchored in the basal body and extending from the apical membrane into the tubular lumen [5]. There is a wide range of cues that can be received by specific ciliary receptors, including photosensation, mechanosensation, osmosensation, and olfactory sensation. Ciliopathies are an emerging class of genetic multisystem disorders that are caused by largely unrelated genes that affect ciliary structures and functions [1]. Over 20 ciliopathies have been identified with an estimation of 1 in 1000 people affected [2]. Ciliopathies cause renal involvement in different ways. Nephronophthisis, the most common genetic cause of end-stage renal disease in children and younger adults, is assumed to be a ciliopathy. Many researchers have shown the role of ciliary dysfunction in renal cystic diseases [3]. Cilia are important during the development of the heart [4].

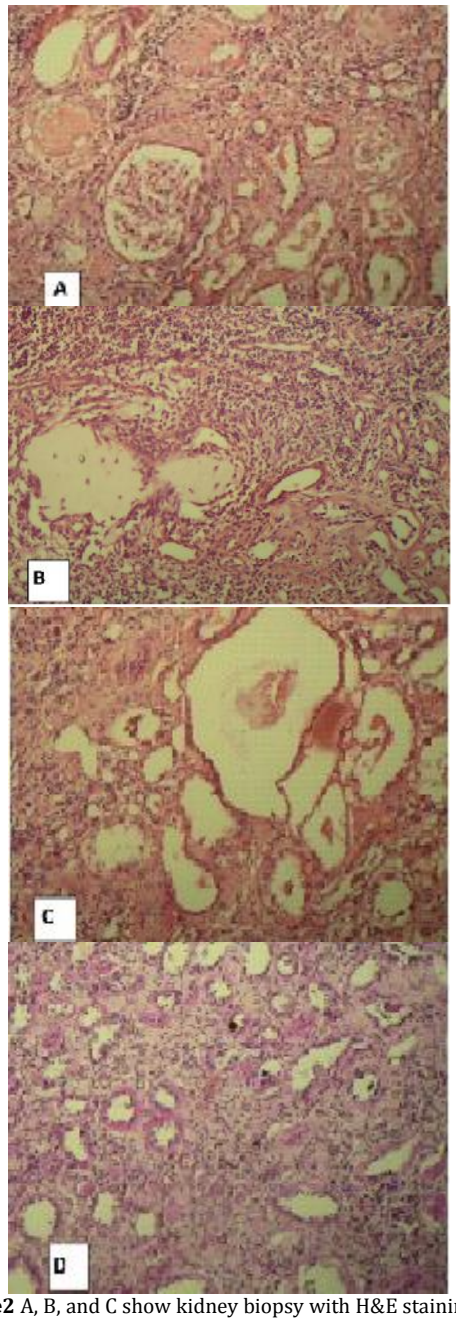

Figure2 A, B, and C show kidney biopsy with H&E staining and D shows kidney biopsy with periodic acid Schiff (PAS) staining revealing interstitial fibrosis, mild focal chronic interstitial inflammation, tubular atrophy and thickening and lamellation of the tubular basement membrane, consistent with nephronophthisis

Hildebrandt et al reported an association between ciliary dyskinesia and congenital heart diseases such as ventricular septal defect (VSD) [1].Other studies have shown that ciliary dysfunction leads to left– right asymmetry, e.g. situs inversus [10]. In 2010, Rajesh Ramineni et al. reported a case of coexistent non-compaction of the left ventricle

and polycystic kidney disease and discussed that this association raised the possibility of an autosomal dominant mutation [11]. In 2012, Kihoonkino and his colleagues published a case in whom non compaction of the left ventricle coexisted with polycystic kidney disease and bronchiectasis. They discussed that abnormal polycystin function in PKD could alter the ciliary response in ciliated cells of the respiratory tract and impair air way clearance [3]. Alternatively, airway dilation in PKD may be due to abnormal polycystines in the smooth muscle, which are thought to contribute to cardiovascular manifestations [6,11]. Boulter et al showed that homozygous deletion of the genes responsible for PKD was also linked to disorganized myocardial arrangement suggestive of left ventricular non compaction in experimental animals [12].

Conclusion

Our reported case had nephronophthisis and left ventricular non compaction. To the best of our knowledge, there is no report of this combination in the literature, which suggests that left ventricular non compaction may be another presentation of cilia involvement. The clinical coexistence of LVNC and nephronophthisis could guide us to better localize and discover the underlying genetic mutations and the role of ciliopathies in various human diseases. Therefore, further research with a special focus potential common derangement of cilia and protein products in these diseases is recommended.

Acknowledgment

We acknowledge Dr. Arash Dehghan for his helpful cooperation in pathologic review of this case

Conflict of Interest

None declared

Financial Support

None declared

References

1. Hildebrand F, Attanasio M, Otto E. Nephronophthisis: Disease Mechanisms of a Ciliopathy. American Society of Nephrology 2009;20: 23–35.
2. Hildebrandt F: Juvenile nephronophthisis. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, editors. Pediatric Nephrology. 6th ed. Berlin Heidelberg, Springer-Verlag 2009; P 831-844.
3. Ki Hoon K, Bong Gun S, Man Je P, Hyoun Soo L, Woo Jung C, Ju Hyeon O: Noncompaction of the Myocardium Coexistent with Bronchiectasis and Polycystic Kidney Disease, Heart, Lung and Circulation 2013;22:312–314.
4. Hildebrandt F, Otto E: Cilia and centrosomes: A unifying pathogenic concept for cystic kidney disease? Nature Reviews Genetics2005;6:928–930.
5. Ergul Y, Nisli K, Bilge AK, Dindar A: Aborted sudden cardiac death in a child with left ventricular non-compaction. Pediatr Int 2013 Jun;55(3):388-91.
6. Vatta M, Mohapatra B, Jimenez S: Mutations in Cypher/ZASP in patients with dilated cardiomyopathy and left ventricular non-compaction. Journal of the American College of Cardiology 2003;42(11):2014–27.
7. Captur G, Nihoyannopoulos P. Left ventricular noncompaction: genetic heterogeneity, diagnosis and clinical course. Int J Cardiol 2010;140:145–53.
8. Bhatia NL, Tajik AJ, Wilansky S, Steidley DE, Mookadam F. Isolated noncompaction of the left ventricular myocardium in adults: a systematic overview. J Card Fail 2011;17:771–8.
9. Kwiatkowski D, Hagenbuch S, Meyer R: A Teenager with Marfan Syndrome and Left Ventricular Noncompaction. Pediatr Cardiol 2010;31:132–135.
10. Mc Grath J, Somlo S, Makova S, Tian X, Brueckner M: Two populations of node monocilia initiate left-right asymmetry in the mouse. Cell 2003;114:61–73.
11. Ramineni R, Merla R, Chernobelsky A. Noncompaction of Ventricular Myocardium Associated With Hypertrophic Cardiomyopathy and Polycystic Kidney Disease. The American Journal of the Medical Sciences 2010;339(4):383-86.
12. Boulter C, Mulroy S, Webb S, Fleming S, Brindle K, Sandford R. Cardiovascular, skeletal, and renal defects in mice with a targeted disruption of the Pkd1 gene. Proc Natl Acad Sci U S A 2001;98:12174–9.