Abstract

Nephroophthisis is an autosomal recessive cystic kidney disease that contributes the most frequent genetic cause of End stage kidney disease (ESKD). It is a rare disorder that affects 9/13 million and accounts for 10-25% of these patients. There are three clinical forms of Nephroophthisis which have been distinguished depending upon the onset of ESKD- 1) Infantile, 2) Juvenile and 3) Adolescent which manifests ESKD at the age of 1, 13 and 19 years respectively. We report an autopsy case in 11 years old boy that had history of chronic kidney disease. The gross examination of bilateral kidneys showed uniform granular and finely scarred surface with adherent capsule at places. Multiple small medullary cysts up to size 8mm were seen on cut-surface. The histological findings of examined slides from the representative’s areas showed extensive sclerosis of glomeruli, peri-glomerular fibrosis, interstitial chronic infiltrate of lymphocytes and few plasma cells. There are also areas showing tubular dilatation and cystic changes involving distal tubules and collecting ducts. Thus findings of gross and histological features confirmed the diagnosis of Nephroophthisis Hence it should always be kept in mind while dealing with ESKD at an early age.

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I. INTRODUCTION

Medullary cystic disease of the kidney was first described in 1945 by Smith and Graham\textsuperscript{1}. Their patient was an eight year boy with an obscure anaemia of insidious onset, severe azotemia, normal urine sediment, no proteinuria, and no personal or family history of antecedent renal disease. At Autopsy, the kidneys contained numerous cysts, one millimetre to one centimetre in diameter, mainly at the cortico-medullary junction, but also in the pyramids and occasionally in the thinned cortices. There was generalized fibrosis and some areas of chronic inflammatory cells. Many glomeruli were hyalinised, but the remainder was either normal or hypertrophied. There was widespread tubular atrophy and dilatation.

A number of similar cases have been reported \textsuperscript{[2,3,4,5,6,7,8,9]}\textsuperscript{. }In 1962 and 1963, Strauss \textsuperscript{[10]} reviewed the available literature and reported two cases of his own plus seven other unpublished cases. In 1966, Goldman et al \textsuperscript{[12]} reported fourteen cases in a single family. In 1951, Fanconi et al \textsuperscript{[12]} described a renal disease that they called familiar juvenile nephroophthisis. The disease was characterized as consisting of anaemia and azotaemia of insidious onset, polyuria, isothenuria, a relative paucity of other clinical findings, and early onset at the age of two to three years, and familiar occurrence. The pathological findings were of contracted kidneys, widespread atrophy of tubules with focal hyperplasia, wide – spread hyalinization of glomeruli, and interstitial round cell infiltrates. Cysts were not consistent findings. Combining data published on both diseases, and recently for the two combined, there have been one hundred and seven well documented cases of this disease reported in the world literature. Priority favours usage of the term medullary cystic disease, but this term is misleading in the light of recent findings and a great deal of confusion exists concerning its application \textsuperscript{[11,13,14,15,16]}\textsuperscript{. }Familiar juvenile nephropathis is also somewhat misleading but is distinctive entity. The abandonment of the modifiers familiar and juvenile would remove the objections to this term. Therefore, I will refer to the herein described disease as nephroophthisis.

Nephroophthisis is an autosomal recessive cystic kidney disease that contributes the most frequent genetic cause of End stage kidney disease (ESKD). Nephroophthisis is a chronic tubule-interstitial nephritis with autosomal recessive inheritance that progresses to ESKD during childhood \textsuperscript{[17&18]}\textsuperscript{. }It is a rare disorder that affects 9/13 million and accounts for 10-25% of these patients\textsuperscript{. }There are three clinical forms of Nephroophthisis which have been distinguished depending upon the onset of ESKD- 1) Infantile, 2) Juvenile and 3) Adolescent which manifests ESKD at the age of 1, 13 and 19 years respectively \textsuperscript{[19]}\textsuperscript{. }The first sign appear after 3 years of age with a urine concentrating defect responsible for polyuria and polydipsia, failure to thrive and progressive deterioration of renal function without signs of glomerular diseases. \textsuperscript{[17&18]}\textsuperscript{. }NPHP 1 gene is responsible for Juvenile Nephroophthisis (type I) \textsuperscript{[20]}\textsuperscript{. }A gene involved in the disease has been mapped out to chromosome 2q13. Homozygous deletions in that region have been detected in 70% of affected children. It is associated with fibrosis and...
scarring of kidney which accounts for the symptoms observed. Some children present with extra – renal symptoms. Nephroophthisis can be associated with taperoretinal degeneration, as in Senior – Loken Syndrome (congenital nystagmus and early blindness). The kidney often has cortico- medullary cysts. Our case is of 11 years boy with history of kidney disease that died. Gross and histological findings in kidneys confirmed the diagnosis of Juvenile Nephroophthisis.

II. AETIOLOGY AND PATHOGENESIS

The most commonly proposed etiologic mechanism of nephroophthisis has been genetic transmission. Two patterns of inheritance have been described. Usually, the familial pattern is most consistent with an autosomal recessive transmission, however, the pattern in some families is more consistent with a dominant. In the families in which autosomal recessive transmission is most with the observed genealogical pattern, the ratio of affected to healthy siblings is close to 1:1. On theoretical grounds this ratio should be 1:3. Since most of these families have been reported as familial juvenile nephronophthisis, as certain bias due to exclusion of sporadic cases may account for this discrepancy, although, as Mangos et al. show statistically, this does not fully explain the disparity between the expected and observed ratios. Decreased concentrating ability of the "kidney in several otherwise healthy relatives of affected patients has been reported in three families. The pedigrees of these families have otherwise been consistent with autosomal recessive transmission. This finding has been considered by several authors to indicate a heterozygous "carrier" state. Careful studies of other families have not documented this finding. Several authors suggest that nephroophthisis represents a primary tubular disease, with interstitial and glomerular change. Herdman et al. proposed that some inborn error of metabolism causes functional and ultimately structural changes in the distal nephron leading to cyst formation and secondarily to glomerular changes and scarring. Mongeau and Worthen noting the histological and clinical features of this disease to be very similar to those of toxic nephropathies, propose that nephronophthisis results from the action of a nephrotoxic substance on the kidney. Because of the probable "genetic nature of the disease, they further postulate that it is a metabolic error that either allows a toxic substance to accumulate or deprives the kidneys of an essential substance. As support for this proposition, relay site the demonstration by Kline et al. that the chronic administration of diphenylamine to rats leads to a disease resembling polycystic disease. They further speculate that some cases of nephroophthisis may be due to exposure to an exogenous toxin.

III. CASE REPORT

We report a case in 11 years old boy that had history of chronic kidney disease. Since this was an autopsy case we could not trace out the details. The gross examination of bilateral kidneys showed uniform granular and finely scarred surface with adherent
Multiple small medullary cysts up to size 8mm were seen on cut-surface. (Figure 2). The histological findings of examined slides from the representative’s areas showed extensive sclerosis of glomeruli, peri-glomerular fibrosis, interstitial chronic infiltrate of lymphocytes and few plasma cells (Figure 3). There are also areas showing tubular dilatation and cystic changes involving distal tubules and collecting ducts (Figure 4). Thus findings of gross and histological features confirmed the diagnosis of Nephroophthisis.

Figure 1: Bilateral kidneys showed uniform granular and finely scarred surface with adherent capsule at places.

Figure 2: Multiple small medullary cysts up to size 8mm were seen on cut-surface.

Figure 3: Showing extensive sclerosis of glomeruli, peri-glomerular fibrosis, interstitial chronic infiltrate of lymphocytes and plasma cells.

Figure 4: Showing tubular dilatation and cystic changes involving distal tubules and collecting ducts.
IV. DISCUSSION

Juvenile Nephroophthisis is the juvenile form of Nephroophthisis that causes ESKD around the age of 13 years [29]. The small medullary cysts, which are constant findings in PM examination, are not a feature of CGN and CPN. USG reveals cysts at the corticomedullary junction within kidneys of normal or slightly reduced size. Cysts tend to develop by loss of normal renal tissue [30]. This is in contrast to polycystic kidney disease of childhood in which kidneys are enlarged with diffuse replacement of renal parenchyma by thousands of micro cysts however the reniform outline of kidney is [31].

Previously Nephroophthisis was grouped with medullary cystic kidney disease due to similar clinical and pathological features. But medullary cystic kidney disease (MCKD) manifests in the 4th decade, 50% cases are associated with renal calculi [32,33,34 & 35]. Nephroophthisis has a mild nature of symptoms and lack of oedema, hypertension or urinary tract infection, resulting in delay in the diagnosis [36,37]. The risk of death is mainly due to electrolyte and fluid imbalance. Pre-natal genetic counselling and testing is the earliest way to detect this condition. Dialysis and symptomatic therapy remains the mainstay of treatment as it is a genetic abnormality1.

V. CONCLUSION

Nephroophthisis is a rare genetic disease associated with ESKD with a poor clinical outcome and limitations related to therapy. It mostly remains misdiagnosed due to silent clinical presentation and findings mimicking other cystic disorders. Hence it should always be kept in mind while dealing with ESKD at an early age.

VI. REFERENCES

Juvenile Nephroophthisis with review of literature along with an Autopsy case report


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