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POLYCYSTIC KIDNEY DISEASE IN A PATIENT WITH ACHONDROPLASIA: CASE REPORT

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SUMMARY

Autosomal dominant polycystic kidney disease is a multisystem disease involving many organs. An association with other diseases such as tuberous sclerosis, von Hippel-Lindau disease and Marfan syndrome have been previously described. We describe a 35 year old female with achondroplasia who developed polycystic kidney disease involving both kidneys and progressing to end-stage renal disease. To the best of our knowledge this is the first such case described in the literature. We also delve, briefly, into the possibility of the genes and chromosomes involved in Marfan syndrome, polycystic kidney disease, tuberous sclerosis and achondroplasia playing a role in the co-occurrence of these entities.

INTRODUCTION

Achondroplasia is the most common form of disproportionate short stature(1). It is an autosomal dominant disorder, but approximately 75% of cases represent new dominant mutations. It is caused by a mutation in fibroblast growth factor receptor 3(FGFR3) on chromosome 4(2). The average adult height of an achondroplasic is about 130cm in men and 123cm in women(3). Other features include disproportionate short stature with a normal trunk length and rhizomelic shortening of the extremeties, macrocephaly, frontal bossing with a depressed nasal bridge, bowing of the lower extremeties, trident hands, lumbar lordosis, infantile hypotonia with motor delays and normal intelligence. The most common complication occurring in adulthood, is related to lumbosacral spinal stenosis with compression of the spinal cord or nerve roots(4). To the best of our knowledge no previous report of an association with polycystic kidney disease exists, hence our report.

CASE REPORT

L.M., a 35 year old female was first seen at the Kenyatta National Hospital in March 1999 complaining of right loin pain, fever and dysuria for a duration of two weeks. The pain was persistently present and not colicky in nature. There was no associated haematuria. Previous to this, she had been perfectly well except for the short stature which had been present from childhood. The rest of the history was none contributory. Physical examination then revealed a sick looking young lady with a temperature of 38.5°C. She was noted to be of a short stature, measuring 123cm in height (Figure 1).

Figure 1

Short stature, 123cm in height

Per abdomen, there was tenderness in both loins, right greater than left. There were no organs or other masses palpable. The rest of the physical examination was unrevealing. A urine culture grew *Escherichia coli* sensitive to several antibiotics and was thus appropriately treated. Her serum urea, creatinine, electrolytes and full blood count were normal. A renal ultrasound done at this time showed a normal left kidney and a cystic right kidney, to rule out moderate hydronephrosis (Figure 2). An intravenous urogram done to rule out the latter showed no dilatation of the collecting system.

The patient was discharged, but got lost to follow up. She presented again to the hospital at the end of January 2002. With a history of exertional dyspnoea and bilateral swelling of the legs for a period of two months. During the same period, she had an accompanying cough and abdominal swelling. She had anorexia, nausea and was vomiting on and off. On physical examination, she was noted to be tachypnoeic

with a respiratory rate of 42/min. She had marked bipedal oedema and pale. In the cardiovascular system, she had a pulse rate of 122/min, regular and of good volume. The blood pressure was 170/115 mmHg and she had an elevated internal jugular venous pressure. Both heart sounds were heard and normal without any murmurs. She had bibasilar crackles in both lung fields, but no other added sounds. Per abdomen, she had marked ascites with a tender hepatomegaly, 11cm below the coastal margin along the midclavicular line. The neurological examination was unrevealing.

Figure 2

Ultrasound of the kidneys when first seen. Normal left kidney, cystic right kidney

Investigations revealed a haemoglobin of 7.9g/dl, blood urea nitrogen of 33mmol/1, serum creatinine of 1394 μmol/l with normal electrolytes and liver function tests. The renal ultrasound this time round showed multiple cysts in both kidneys, those on the right kidney being larger than those on the left with considerable damage to the parenchyma on both sides (Figure 3).

Figure 3

Ultrasound of the kidneys at the second presentation. Both kidneys multicystic, cysts in the right kidney much larger than those on the left

The chest X-ray showed cardiomegaly with congested lung fields, features in keeping with heart failure. She had a moderate pericardial effusion on echocardiography with low voltage tracings on electrocardiography.

She was started on intravenous frusemide 80mg daily and captopril 50mg thrice daily before the initiation of maintenance haemodialysis on which the patient stabilised and is continuing on a thrice weekly, four hourly, regimen.

DISCUSSION

We report on a 35 year old female with achondroplasia and polycystic kidney disease leading to end-stage renal disease. To the best of our knowledge, this is the first such case reported in the literature.

Autosomal dominant polycystic kidney disease (ADPKD), characterised principally by bilateral renal cystic enlargement, is one of the most common dominantly inherited conditions and is an important cause of chronic renal failure(5). It is now appreciated to be a multisystem disease, with cysts and connective tissue abnormalities involving many organs(6). Thus, cardiac valve abnormalities, intracranial aneurysms, intestinal diverticuli and hernia of the abdominal wall all occur with increased frequency. There are also several reports of ADPKD associated with connective tissue features reminiscent of Marfan syndrome (MFS) and congenital contractual arachnodactyly (CCA) in addition to other autosomal dominant inherited diseases like tuberous sclerosis and von Hippel-Lindau disease(7,8). Although ADPKD is caused by mutations in at least three different genes, most affected families have polycystin -1 abnormalities attributable to mutations in the PKD 1 gene located on chromosome 16, while most of the other cases are due to polycystin-2 anomalies caused by mutations within PKD 2 gene on chromosome 4(9). In this context, it is worth noting that achondroplasia is caused by a mutation in FGFR3, a gene also located on chromosome 4 as is PKD 2 gene. This in itself is not enough to explain the co-occurrence of these two entities considering that PKD 2 gene is located at chromosome 4q21-4q23 while FGFR3 gene is at 4p16.3 (10), loci which are far apart on the chromosome, although translocations could still bring them closer. Because the prevalence of ADPKD in the population is around 1 in 1000(11) and the prevalence of achondroplasia is known to be a minimum of 1 in 15,000(1), the chance of an individual having both ADPKD and achondroplasia is approximately 1 in 15 million.

Considering other disease states that have co-occurred with ADPKD, Marfan syndrome is an autosomal dominant disorder involving mainly the ocular, cardiovascular and skeletal system and is caused by mutations within Fibrillin -1 gene located on chromosome 15(12) while mutations in Fibrillin -2 gene located on

chromosome 5q23 is responsible for congenital contractual arachnodactyly (CCA), another connective tissue disorder with similar features to Marfan syndrome(13). In as much as the association between MFS and CCA with ADPKD has been attributed to chance by others(14), the proximity of the chromosomes involved viz. 16 and 4, for ADPKD 1 and ADPKD 2 respectively to those of MFS and CCA, is worth noting and chromosomal crossovers cannot be ruled out. In tuberous sclerosis, large deletions, disrupting PKD 1 and the adjacent tuberous sclerosis type 2 gene (TSC 2) occurs, resulting in tuberous sclerosis and severe, childhood-onset polycystic kidney disease(15). So far, this has been the only clear description of a genotype/phenotype correlation in ADPKD and there are no reports of specific PKD 1 or PKD 2 mutations specifically predisposing to additional connective tissue abnormalities.

In conclusion, we report a co-occurrence of achondroplasia with polycystic kidney disease and in as much as chance could be the major player in this, considering the dearth of literature relating to this, we bring in some molecular basis of these diseases which would be worth looking into.

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