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PITFALLS IN THE DIAGNOSIS OF NEPHRONOPHTHISIS

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ABSTRACT

Juvenile NPHP, the most common form of the disease, initially manifests at around age 5-6 with polyuria and polydipsia. These symptoms are consequent to a decreased urinary concentrating capacity and loss of sodium conservation and occur early in the course of the disease. Nighttime fluid intake and salt craving are characteristic features of the patient's history. Secondary nocturnal enuresis may eventuate. As these features develop well before any reduction in glomerular filtration rate, are non-specific and of a mild nature, they often mask the underlying disease.We report a case of juvenile NPHP in a 15 year old female in which diagnosis was only established when she presented with end stage renal disease. The patient's course and reasons for the deferred diagnosis are discussed.

INTRODUCTION

Nephronophthisis (NPHP), an autosomal recessive cystic kidney disease, is characterized by the insidious onset of renal failure in children and young adults. The incidence of NPHP has been estimated to range from 1 in 50,000 to 900,000 live births and the prevalence within the pediatric population with end-stage renal disease in the U.S is 5% [1,2]. It presents equally in males and females. Three clinical variants have been described based on the median age of onset of end-stage renal disease: infantile (one year of age), juvenile (13 years of age), and adolescent (19 years of age). Patients with NPHP have mutations in genes of the ciliary apparatus and the clinical variants are associated with unique mutation profiles of 13 known genes [3].

These mutations are thought to impair concentrating ability and regulation of luminal flow in the nephron, leading to dysregulated tissue growth and the development of renal cysts [4,5]. Expression of NPHP genes in other organ tissues leads to extra-renal manifestations such as retinitis pigmentosa, hepatic fibrosis, skeletal defects, situs inversus and septal cardiac defects [6].

The earliest presenting symptoms of NPHP are polyuria, polydipsia, nocturia and secondary enuresis. Clinical findings related to progressive chronic kidney disease such as anemia, metabolic acidosis and growth retardation develop later in the course of the disease. Because of the mild nature of the initial symptoms, there is often a delay in the diagnosis of NPHP. We report a case of juvenile NPHP in a 15 year old female in which diagnosis was only established when she presented with end stage renal disease. The patient's course and reasons for the deferred diagnosis are discussed.

CASE DESCRIPTION

A 15-year-old Arab girl presented to the pediatric emergency room with complaints of weakness, chest pain, dyspnea, and fatigue upon exertion notable for the past two weeks. In the days prior to her presentation, she noticed a sharp decrease in appetite, nausea, andoliguria. During the

preceding two weeks she had persistent menstrual bleeding. The patient is the fourth living child of six siblings to consanguineous parents (first degree cousins). Two younger brothers aged 10 and 14 have, respectively, been diagnosed with autism and attention deficit disorder. Her three elder brothers aged 28, 26 and 23, are healthy. One other brother had died in infancy (15 months) having suffered from growth retardation. The parents denied any family history of renal disease.

The patient reported that from an early age she had experienced intense thirst compensated for by a large daily fluid intake. At the age of 13, she developed nocturnal enuresis for which she was offered desmopressin but did not take the medication. For the six months prior to her admission she had mainly subsisted on drinking four to five cans of a caffeinated energy drink per day and eating lemons with salt.

On examination she appeared pale, was fully conscious and oriented to time and place. Body weight was 44Kg. Her temperature was 36.9 °C, pulse 117 beats/minute, blood pressure 127/73 mmHg and she was mildly tachypnea at 20-25 breaths/minute. She appeared to be euvolemic. There were no uremic signs such as a flapping tremor or pericardial rub.

Laboratory data showed Hb 3.1 g/dL, MCV 75fL, MCH 23.1 pg, WBC 8670/µl, platelets 284 K/µl, urea 194 mg/dL, creatinine 11.1 mg/dL, Na 140 mEq/L, K 5.0 mEq/L, Cl 104 mEq/L, calcium 5.5 mg/dL with an ionized calcium of 2.8 mg/dl and phophorus 11 mg/dL.A blood smear revealed microcytosis, individual schistocytes, and basophilic stippling. Cholesterol, triglycerides and liver enzymes were within normal limits. Beta-HCG testing was negative, a coagulation screen was normal. Coombs test was negative. A 24 hour urine collection for protein measured 1653 mg. Urine output was estimated around 1.5 ml/kg/hour. Blood gases analysis showed a pH of 7.39, pCO_2 36 mmHg and HCO_3 21.8 mEq/L. Serologies for hepatitis B, hepatitis C, and CMV were negative. Results for EBV indicated past infection.

On renal sonography the kidneys were moderately reduced in size, hyperechoic with corticomedullarymicrocysts.

End stage kidney disease due to NPHP was diagnosed and the patient transfused and prepared for dialysis.

DISCUSSION

This female patient presentedat 15 years of age with end stage renal disease. Prior to presentation renal failure had been unsuspected. However, reviewing her history, it should have been considered. The anamnestic hints pointing to an underlying renal disease included parental consanguinity, the onset of polydipsia and polyuria at an early age, secondary nocturnal enuresis at age 13 and the patient's salt craving. These features are characteristic of juvenile NPHP, an autosomal recessive disease. Whilst it is true that they begin to manifest in childhood (age 5-6 years) well before any perceivable decline in GFR, their persistence behoves the wary physician to closely monitor renal function during the ensuing years.

Our patient's extreme anemia was due to a combination of her renal failure and prolonged menorrhagia. NPHPis typified by the disproportionate severity of anemia in relation to the degree of renal dysfunction Menorrhagia was probably worsened by the thrombocytopathy associated with advanced renal insufficiency [5-8].Despite NPHP being a salt losing state, the patient managed to remain euvolemic due to her avid drinking and dietary salt craving. With this degree of renal impairment, one would have expected a severe metabolic acidosis rather than the normal acid/base profile seen in our patient [4-8]. We postulate that the vast amount of lemons consumed by our patient provided a bicarbonate precursor in the form of citrate, therefore neutralizing acid/base status.

In conclusion, although juvenile NPHP may be difficult to diagnose particulary at an early age, the features outlined above should alert the physician to its possible occurrence. A presumptive diagnosis can be made based on the clinical presentation (symptomatology as described above) and the sonographic findings. Definitive diagnosis can be ascertained by genetic testing [9]. Our patient is now on chronic hemodialysis awaiting transplantation. The prognosis for NPHP patients after transplantation is favorable when compared to the overall pediatric kidney transplant population[10].

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CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

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