Familial Juvenile Hyperuricemic Nephropathy 1 (FJHN1)

Rajat Bhargava1, Renu Saigal2, Rajeev Sharma3, Laxmikant Goyal4, Abhishek Agrawal5

Abstract
Familial juvenile hyperuricemic nephropathy 1 (FJHN1) is an autosomal dominant disorder characterized by decreased urinary excretion of urate and hyperuricemia, followed by the development of chronic interstitial nephritis most often leading to progressive renal failure and death in middle age. We report a case of FJHN1 presenting as chronic tophaceous gout, hypertension, renal failure and a family history suggestive of autosomal dominant inheritance, for its rarity.

Introduction
Urate is an end product of purine metabolism in humans who have lost the expression of uricase gene during evolution. Urate is freely filtered by glomerulus and essentially reabsorbed, as only ten percent of the filtered load is present in the final urine. Urate is reabsorbed mainly by URAT1 exchanger in the proximal convoluted tubules. Increase in urate levels above 6.8mg/dl is termed hyperuricemia. It may be due to urate overproduction or underexcretion.

Familial juvenile hyperuricemic nephropathy 1 (FJHN1) is an autosomal dominant rare disorder; only fifty families have been reported in world so far, no case reports are available from India. Locus for this disorder is located on chromosome 16p12. Gene responsible is UMOD gene encoding the uromodulin protein. Mutation in this gene leads to accumulation of abnormal uromodulin protein leading to decreased urate excretion, hyperuricemia and chronic progressive interstitial renal disease leading to death in middle age. Laboratory investigations show hyperuricemia and reduced fractional clearance of uric acid.

We report a case of chronic tophaceous gout, in a young male with hypertension, hyperuricemia, renal failure, reduced fractional clearance of uric acid and a family history suggestive of autosomal dominant inheritance. All of the findings suggest Familial juvenile hyperuricemic nephropathy probably type 1 as there is late onset of anemia.

Case Report
A thirty year old Sikh male, resident of Haryana, laborer by occupation admitted in November 2011 with recurrent arthritis of ankles, knees, wrists, elbows, metatarsophalangeal joints of big toe for the last ten years, involving one joint at a time initially. At the beginning patient had pain and swelling in right ankle joint, then right metatarsophalangeal joint and later involving other joints. Since last five years patient had developed chronic polyarthritis of all joints involving small joints of hands and feet. His axial joints were spared. Mobility of joints was restricted with gross deformities of fingers and toes. During last five years he also had developed multiple firm to hard, painless swellings in and around joints of hands, feet, ankles and wrists. Some of these had spontaneously discharged chalky white material.
Patient had vertigo and headache for last six months, hypertension was detected and patient received treatment for the same. There is no history of fever, inflammatory back pain, cervical pain, bone pain, urinary tract infection, pain abdomen, altered bowel habits, trauma, skin disease, nail disease, oral ulcers, alopecia, malar rash and photosensitivity. Patient was on non-steroidal anti-inflammatory drugs and ayurvedic medicines for last ten years and was referred to a surgeon for foot amputation. He had also received anti hypertensive drugs for last six months.

Patient’s elder sister had similar complaints of recurrent arthritis with renal failure. His father and all his paternal uncles and aunts had died in middle age with joint complaints and renal problem (Figure 1). His mother had no such complaints.

On examination patient was conscious, cooperative, well oriented to time, place and person. Patient was hypertensive with blood pressure 150/80mm Hg right arm sitting position, afebrile and rest of the vitals were stable. Conjunctiva and tongue were pale. There was no cyanosis, clubbing, edema feet, icterus and lymphadenopathy. Respiratory, cardiovascular system, central nervous system and gastrointestinal system was normal.

On musculoskeletal examination axial skeleton was normal. In appendicular skeleton tophi of various sizes were deposited in and around ankle joints, metacarpo-phalangeal joints, metatarso-phalangeal joints, distal inter-phalangeal joints, proximal inter-phalangeal joints of fingers (Figure 2) and toes. Tophi were also found over tendoachilles near ankle joint. Skin overlying tophi on foot and big toe (Figure 3) had desquamated and ulcerated with chalky white discharge. Effusion and tenderness were present in small joints of hands and feet with restriction of range of movement.

**Investigations**

Investigations showed hemoglobin-10.6 gm/dl, total leucocytes count-10,250/mm³ with 82% neutrophils and 16% lymphocytes. TRBC-4.76 million/mm³, MCV-70.0 fl, MCH-22.3 pg, MCHC-31.8 g/dl, RDW-17.0%, PCV-33.3% and platelets 2.68 lacs/mm³. Peripheral blood film showed microcytic hypochromic red blood cells, no immature cells and adequate platelets. ESR was 30mm in 1st hr.Serum urea-75.0 mg/dl (15-45mg/dl), serum creatinine-2.3 mg/dl , s. uric acid-7.1 mg/dl(4-6mg/dl) were increased. Serum calcium-9.3 mg/dl, phosphorus-4.2 mg/dl, serum electrolytes sodium-137.0 meq/L, chloride-99.0 meq/L, potassium-3.9 meq/L and fasting blood glucose-98.0 mg/dl were normal. Serum iron-37.0 µg/dl was reduced with normal TIBC-354µg/dl. Liver function tests, thyroid function tests, lipid profile, Serum proteins, LDH, CPK, alkaline phosphatase were normal. Vitamin B12->1000 pg/ml and folate->24 ng/ml were normal. C-reactive protein (CRP) and rheumatoid factor (RF) were negative. Urine examination showed protein - absent, pus cells- 5-7/HPF, RBCs- 8-10/HPF with no casts. Twenty four hour urinary uric acid excretion was reduced- 264mg (300-750mg).ECG and X-ray chest were normal. X-ray hands (Figure 4) showed right 3rd proximal interphalangeal joint erosions. X-ray feet (Figure 5) showed multiple erosions, well defined with overhanging bony edges (Martel’s sign), soft tissue swellings (tophi) and absence of osteoporosis. USG abdomen showed bilateral medical renal disease with normal kidney size.

On joint aspiration, synovial fluid on light
microscopy showed large number of needle shaped crystals suggestive of mono-sodium urate crystals (Fig.6). FNAC of swellings showed clumps of non cellular needle shaped crystals with foreign body type giant cells suggestive of gouty tophi. On screening of his family members his elder sister had hyperuricemia, gouty arthritis, renal failure and decreased 24hr urinary uric acid excretion. His three younger brothers 20, 23, 25 years old had hyperuricemia, decreased 24hr urinary uric acid excretion- 193mg, 230mg, 208mg respectively but without arthritis and renal failure, showing that hyperuricemia is because of underexcretion per se. His paternal cousins also had hyperuricemia with renal failure. Three members of the next generation also had asymptomatic hyperuricemia of underexcretory type, rest others are to be screened. Such a pattern was suggestive of autosomal dominant (AD) type of inheritance.

Familial hyperuricemia is due to (a) Overproduction of uric acid as seen in Lesch Nyhan Syndrome (Complete deficiency of enzyme HPRT), Kelly Seegmiller Syndrome (Partial deficiency of enzyme HPRT), PRPP Synthetase Overactivity, characterized by hyperuricosuria and are X-linked in inheritance.

(b) Underexcretion of uric acid as seen in Familial juvenile hyperuricemic nephropathy 1 (FJHN1), Familial juvenile hyperuricemic nephropathy 2 (FJHN2), Medullary Cystic Kidney Disease 2 (MCKD2), characterized by reduced fractional clearance of uric acid and are autosomal dominant in inheritance.

Familial juvenile hyperuricemic nephropathy 1 is a rare disease, autosomal dominant in inheritance. First described in 1960 by Duncan and Dixon, fifty families reported in world so far. Chromosome 16p12 and UMOD gene is involved. Mutations of the UMOD gene lead to defect in uromodulin tubular proteins resulting in under excretion of uric acid seen before puberty. Hyperuricemia and gout develops after adolescence and progressively renal functions deteriorate and end stage renal disease develops within ten to twenty years. On histopathological examination, renal tissue shows chronic tubulointerstitial nephropathy with focal interstitial fibrosis and inflammatory cell infiltration. Investigations show hyperuricemia, reduced fractional clearance of uric acid and late onset of anemia.

FJHN disease is defined by following criteria: (Dahan et al – Ref. 1.) 1. History of CRF in at least two related family members with an inheritance compatible with autosomal dominant trait. 2. Exclusion
of other well defined hereditary nephropathy.

3. History of gout or hyperuricemia in all individuals with CRF.

In our case patient had chronic polyarticular tophaceous gout, hypertension, renal failure (serum creatinine - 2.3 mg/dl), raised uric acid levels (7.1mg/dl) and reduced 24hr urinary uric acid excretion (264mg). X-rays were suggestive of chronic tophaceous gout, USG showed bilateral medical renal disease without corticomedullary cysts. Joint fluid aspirate showed inflammatory arthritis and mono sodium urate crystals. His father and paternal uncles died at middle age (40-50yrs) due to renal failure. His elder sister and all 3 younger brothers had hyperuricemia and decreased 24hr urinary uric acid excretion. The family history was suggestive of autosomal dominant inheritance. Definitive diagnosis is made by investigations which are: Urinary wild type uromodulin levels, renal biopsy showing tubular cell expression of uromodulin and genetic studies in form of mutational and linkage analysis. Familial juvenile hyperuricemic nephropathy type 2 is similar to FJHN1 but REN gene is involved and there is early onset of anemia in infancy. Medullary Cystic Kidney Disease 2 (MCKD2) has similar picture but USG shows multiple corticomedullary renal cysts.

All of the findings suggest Familial juvenile hyperuricemic nephropathy probably type 1 as there was late onset of anemia and USG showed no corticomedullary renal cysts. So it was a diagnosis of exclusion as urinary wild type uromodulin levels, renal biopsy for tubular cell expression of uromodulin and genetic studies in form of mutational and linkage analysis was not possible in India.

Patient was prescribed tablet paracetamol (500mg TID) and tramadol (50mg SOS) for pain relief. Non-steroidal anti-inflammatory drugs were not given due to renal failure. Antibiotics were given to prevent secondary infection of burst tophi. Losartan (50mg OD) was started as antihypertensive and later dose was increased (50mg BD). Colchicine was given in low doses (0.5mg ½ OD) because of renal failure. Patient was started on Febuxostat (20mg OD increased to 60mg) to reduce uric acid levels. Patient was also given Iron tablets and intramuscular steroids (depot methylprednisolone 80mg) to reduce joint pain and swelling. Patient was advised to take plenty of fluids and avoid alcohol and meat consumption. Patient improved and joint swelling subsided. After seven months there were no new tophi and he has had no more gouty attacks.

References