Partial HPRT Deficiency (Kelley - Seegmiller Syndrome)

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Abstract
Hypoxanthine – guanine phosphoribosyl transferase (HPRT) deficiency is an X-linked defect of purine metabolism. Clinical manifestations are usually related to the degree of enzyme deficiency; complete HPRT deficiency (Lesh-Nyhan Syndrome) presenting with severe neurological or renal symptoms, or partial HPRT deficiency (Kelley-Seegmiller syndrome) manifesting as a gout-urolithiasis syndrome. We report a case of partial HPRT deficiency presenting as chronic tophaceous gout, mental retardation, nephrolithiasis and family history suggestive of X-linked inheritance, for its rarity.

INTRODUCTION
Hypoxanthine – guanine phosphoribosyl transferase (HPRT) is a ubiquitous, cytoplasmic, housekeeping enzyme with highest activity in the brain and testes. HPRT catalyzes the transfer of the phosphoribosyl moiety of PP-ribose – P to hypoxanthine and guanine, forming inosine monophosphate and guanosine monophosphate, respectively. Inability to recycle hypoxanthine and guanine produces a lack of feedback control of synthesis accompanied by rapid catabolism of these bases to uric acid (Fig. 1). HPRT deficiency is an X-linked defect (Xq26-q27.2) of purine metabolism with considerable genetic and clinical heterogeneity, the biochemical hallmark being increased levels of uric acid in blood and urine. Clinical manifestations are related to the degree of enzyme deficiency, complete HPRT deficiency (Lesch-Nyhan disease; LND) presenting with severe neurologic (choreoathetosis, self mutilation), gout and renal symptoms. Partial HPRT deficiency (Kelley – Seegmiller syndrome) has a broader spectrum of presentations ranging from gout and urolithiasis only, to intermediate forms characterized according to the severity of neurologic involvement.

We report a case of chronic tophaceous gout, in a young male with mental retardation, nephrolithiasis and a family history suggestive of X-linked inheritance. Based on this we presumed that our case had partial HPRT deficiency. We could not confirm the diagnosis as HPRT levels in lysed and intact RBC as the tests are not done in the India and only available abroad at a very high cost which our patient could not afford.

CASE REPORT
A 23 years old male was admitted on July 2003 with recurrent arthritis of both ankles, knees, wrists, elbows and metatarso phalangeal joints (MTP) of big toe since last 4 years, involving one joint at a time. Since the last one year patient had developed chronic polyarthritis of all joints including small joints of hands and feet. His axial joints were spared. Mobility of joints was restricted with gross deformities of fingers and toes. During the last one year, he also had developed multiple firm, painless swellings in and around joints of hands, feet, ankles, wrists and also over forearms, legs and soles. Some of these had spontaneously discharged chalky white material. He also had low grade continuous fever since 1 year. There was no history of self mutilation, morning stiffness, photosensitivity, genitourinary complaints, red eye, or Raynaud’s phenomenon. Patient was on prednisolone 20 mg, since six months and repeated incisions and drainage of swellings had been performed. Patient’s younger brother had history of recurrent nephrolithiasis of both kidneys for which pyelolithotomy was performed twice seven and four years ago respectively. His maternal uncle died at young age due to renal problem. Both of his sisters were asymptomatic.

On examination patient was conscious, cooperative; vitals were stable. Temperature was 99.8°F. Pallor was present. There was no lymphadenopathy. Respiratory, cardiovascular, central nervous system, gastrointestinal system examination was normal except for mild mental retardation. Intelligence quotient (IQ) was 69.

Musculoskeletal examination showed bilateral olecranon, pre and infrapatellar bursal swellings, tophi
of various sizes were deposited in and around meta-
carpophalangeal (MCP) joints, meta-tarsophalangeal
(MTP) joints proximal interphalangeal joints, (PIP) distal
interphalangeal joints (DIP) of digits and toes, elbow
joints, and ankle joints. Tophi were also found over flexor
tendon sheaths of forearms, extensor tendon sheaths of
wrists and ankles and also over soles of feet. Skin
overlying some of the tophi had desquamated with
chalky white discharge. Effusion and tenderness were
present in knee, ankle, wrist and elbow joints. Range of
movement of almost all the joints except the axial joints
was restricted. PIP of right thumb was grossly destructed.
Investigations showed hemoglobin – 7.2gm/dl, total
leukocyte count – 7.420/mm³ with neutrophils 84%,
lymphocytes 13%; MCV – 103.2fl; MCH – 23.1pg, MCHC
22.4 gm/dl, platelet 4.81 lacs/mm³, PCV 32.2%, TRBC –
3.12 mill/mm³, ESR – 132mm/1 hr. Peripheral blood
film showed macrocytic cells; no immature cells were
seen. Corrected reticulocyte count was 1.2%. Urine
examination showed uric acid crystals (+++). Blood
sugar was 90mg/dl, serum urea - 68 mg/dl (15-45),
serum creatinine was also increased 1.8 mg/dl (0.6-1.6),
serum bilirubin 0.6mg/dl, SGOT/SGPT 74/50 U/L (0-
40/5-36), serum uric acid - 17 mg/dl (4-6), 24 hours
urinary uric acid - 1498 mg (N = 600 mg), serum total
protein 7.0 gm/dl, albumin 4.0gm/dl, globulin 3.0gm/
dl. Serum alkaline phosphatase was 477u/L (110-310
U/L). Bone marrow examination showed megaloblastic
marrow, no atypical cells were present. C-reactive protein
(CRP) was positive, rheumatoid factor (RF) and
antinuclear antibody (ANA) were negative. HIV I and II
were negative by ELISA. His serum iron was 68 µg/dl,
sodium folate - 7.2 ng/ml and vitamin B12 - 680 pg/ml.
Joint fluid aspirate showed WBC – 31,000/mm³, sterile
on culture; polarized microscopy showed large number
of needle shaped crystals with negative birefringence.
X-rays of hands and feet, showed well defined erosions
with overhanging bony edges (Martel’s sign), soft tissue
swelling and absence of osteoporosis. Ultrasonography
of abdomen revealed bilateral nephrolithiasis. His
younger brother was screened. His serum uric acid was
12.0 mg/dl (4-6), 24 hrs urinary uric acid - 1028 mg (up
to 600 mg). RBC HPRT level estimation was not possible.
Identification of molecular genetic mutation in the HPRT
gene was also not possible. His sister’s serum uric acid
level could not be estimated as she was unwilling.

The partial deficiency of HPRT was first reported by
Kelley et al1 in subjects with early onset gouty arthritis
and an increased incidence of urate renal stones. Up to
25% of these patients have minor neurological features,
but do not self-mutilate as in Lesch – Nyhan syndrome
in which the enzyme deficiency in complete.6 There is
markedly increased production of uric acid with daily uric acid excretion in the range of 16-36 mg/kg body weight and serum urate as high as 18 mg/dl. False low urinary uric acid may be seen in acute renal failure and simply measuring uric acid in urine without previous warming and through mixing of the entire 24 hour collection at 56°C. Gout usually develops between 13-20 years of age because there is high uric acid clearance before puberty. It is usually associated with uric acid nephrolithiasis. The excessive production of uric acid characteristic of partial HPRT deficiency results from an accelerated rate of de novo purine biosynthesis. The inheritance is X-linked. Major clinical manifestations are in the affected male with evidence of transmission through carrier females. Patients may have mild mental retardation (IQ 67-75) with macrocytic peripheral blood picture and megaloblastic changes in bone marrow. Vitamin B-12, folate, and iron levels are typically normal. Definitive diagnosis is made by estimating HPRT activity in intact and lysed RBC (0.01-30% of normal). Diagnosis is confirmed by identifying molecular genetic mutation in the HPRT gene. In our case the patient had chronic tophaceous gout very high serum uric acid (17 mg/dl) and 24 hour urinary uric acid excretion (1498 mg) with megaloblastic anemia, mild mental retardation. Bilateral nephrolithiasis and X-rays suggestive of chronic tophaceous gout. Joint fluid aspirate showed inflammatory arthritis and uric acid crystals. His material brother died at younger age due to renal insufficiency and his younger brother had high serum uric acid (12.0 mg/dl) and 24 hours urinary uric acid excretion (1028 mg/dl) and recurrent nephrolithiasis, but no history of gouty arthritis. Both of his sisters were normal. The family history was suggestive of X-linked inheritance. All of the findings suggest partial HPRT deficiency (Kelley – Seegmiller syndrome). RBC HPRT level was not possible. Patient was prescribed NSAID (ibuprofen 400 mg 12 hourly), antibiotics – oral ampicillin 500 mg 6 hourly for 7 (to prevent secondary infection of burst tophi), allopurinol – 100 mg/day with weekly increment of 100 mg. At the time of discharge he was on 300 mg allopurinol. Colchicine 0.6 mg twice a day with urinary alkaliser was also prescribed. He was advised to take plenty of fluids to keep his urine output >2.0 L/day. At the time of discharge his uric acid was 7.0 mg/dl. After...
two months his uric was 4.8 mg/dl, serum urea – 30.0 mg/dl and creatinine 1.3 mg/dl. There were no new tophi and he has had no more gouty attacks.

REFERENCES


Announcement

Dr. JC Patel & Dr. BC Mehta Best Paper - JAPI Awards 2006

Following papers were selected for Dr. JC Patel & Dr. BC Mehta Best Paper awards for articles published in the Journal for the period from 1 October 2004 through September 2005.
6th Joint Prize for 2nd Best Case Report entitled “Tuberculous Skin Ulcer Following Needle-Prick Injury in a Health Care Professional” – A Chandramukhi, MV Manjunath, HB Veenakumari, Anita Mahadevan, G Shivaraja, S Buggi – Departments of Neuromicrobiology and Neuropathology, National Institute of Mental Health and Neurosciences, and Shanthabai Devarao Shivararam Tuberculosis and Rajiv Gandhi Institute of Chest Diseases, Hosur Road, Bangalore 560 029, J Assoc Physicians India 2005;53: (9) 825-826.
7th 1st Prize for Best Correspondence entitled “Atypical Presentation of Visceral Leishmaniasis” – Mala V. Kaneria, S Jagtap, Charu Modi, Sandhya Kamath – Departments of Medicine and Pathology, TN Medical College and BYL Nair Ch. Hospital, Dr. AL Nair Road, Mumbai J Assoc Physicians India 2005;53: (6): 573-575.

All the awards will be presented to recipients at the hands of President of API during the 61st Annual Conference of API during General Body Meeting of API to be held on 30th January 2006 at Patna.

Shashank R Joshi
Hon. Editor