

Hypoxanthine-Guanine Phosphoribosyltransferase (HPRT) Deficiency: Lesch-Nyhan Syndrome

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ABSTRACT

Lesch-Nyhan is a genetic metabolic disease. It involves disorder related to uric acid in which attitude problems are dominant. The changed and wild genes will tell us about this disorder that it is a disorder of X-chromosome. This disease is dominant in men. It involves completely impaired action of HGPRT. In this disease excess quantity of uric acid produced in joints of the body and other parts. It also causes dis functioning of gout. It also causes problems in brain function. It also involves physical disability. The victim of this disease demands for extra care. Different clinical methods and techniques can be used to improve the attitude of the victims suffering from this disease.

Keywords : Lesch-Nyhan, HGPRT, Hyperuricemia

I. INTRODUCTION

Lesch-Nyhan syndrome is a very uncommon X-linked recessive genetic disease that is generally takes place in the male children. Hyperuricemia, spasticity, biting of fingers, mental retardation and hypoxanthine-guanine phosphoribosyltransferase help in the characterization of this disease.

Lesch-Nyhan disease as a model for detecting disorders

Lesch-Nyhan syndrome can be taken as a standard for finding out genotype–phenotype correlations (Jinnah *et al.*, 2000). The cause of this disease is the HPRT1 gene which was also the first gene which was identified for any neurogenetic disorder. The enzyme which is involved in the onset of this disease is hypoxanthine-guanine phosphoribosyl transferase (HGprt) which is known to cause changes in purine metabolism. This enzyme is encoded by the gene which has only a functional messenger RNA transcript present in it. HPRT1 gene is known to have been causing a number of mutations. These mutations include splicing mutations, nonsense mutations, missense mutations, non coding regulatory changes, tiny and huge coding and non-coding deletions or insertions, small mutations and

difficult regulations. The onset of the disease is primarily due to the mutation of HPRT1 gene on HGprt enzyme activity (Jinnah *et al.*, 2000). However, quite a number of latest disorders-produce changes in genome have also been known, recently.

Phenotypically, the long-established clinical definition of Lesch-Nyhan disorder can be described by motor unfunctioning, excess amount of uric acid, intellectual affliction, and complication relating to the behaviour e.g self-injurious behavior (Lesch *et al.*, 1964; Jinnah *et al.*, 2006). However, it has also been found that some of the above clinical symptoms are either clinically insignificant or entirely absent in clinical attenuated variants (Puig., 2007). Such victims with impaired physical composition are designated as Lesch-Nyhan modification. Patients with not very serious symptoms of such variants can be described by the uric acid overproduction. Patients with such mild variants usually do not show such plainly apparent neurological abnormalities or disturbed behavioral problems, and generally are recognised as patients having HGprt-related hyperuricemia (HRH). Both the class of patients that show extreme phenotypes of Lesch-Nyhan disorder as well as those that have HRH disorder, also designated as HGprt-related neurological dysfunction (HND) depicts a range of physical composition having different

point of brain performance disabilities. HND carriers do not show harmful attitude as usually observe in the case of classic Lesch-Nyhan disease. However, they do show some symptoms such as plenty of production of uric acid together with some other performance problems (Nyhan., 2000).

HPRT1 gene and HGprt enzyme

The human X chromosome has been known to contain the HPRT1 gene in the area q26-27. A single mature messenger RNA is encoded by HPRT1 gene. The messenger RNA, containing eight introns and nine exons is 1.6 kb in size. This messenger RNA aids the formation of HGprt protein with the help of a coding region containing 654 nucleotides. The molecular weight of HGprt protein is 24.6 kD. A number of different forms of the clear form of HGprt protein have been reported. These include its free form, forms liganded with its inosine monophosphate or guanosine monophosphate (GMP) output, or forms tangled with a transformation condition similar to pyrophosphate. The study of its core structure proves that the enzyme contains five parallel beta-sheets which are bounded by four alpha helices. hinge on the ionic bond of the solvent the HGprt protein gathered simultaneously as either a dimer or tetramer of similar parts. Salt bridges, hydrophobic interactions and hydrogen bonds aid in the bounding of the subunits. The following figure shows subunits from A to D. It shows that most of the interactions happen to take place between A-B and A-C interfaces while A-D interface experiences the least interactions. Four domains are involved in the catalytic reaction of the HGprt protein. These include three loops which are involved in forming the catalytic parts while another large loop that almost completes the process (Fig. 1). A number of conformational changes take place during this catalytic cycle. The HGprt's structure and function provides an excellent source for precisely describing the effect of mutations on the function of enzyme and the reason for causing clinical manifestations (Aral *et al.*, 1996).

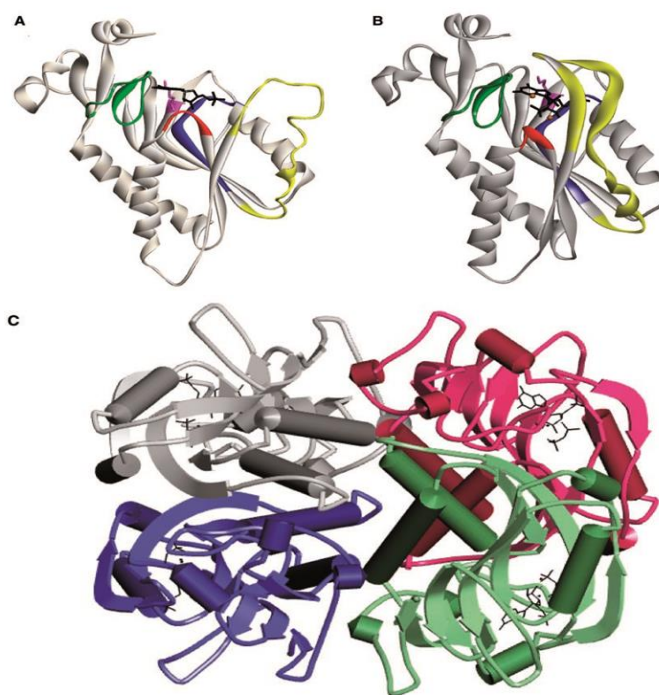


Figure 1. The Ribbon diagram for human HGprt

The phosphate bonds of phosphoribosylpyrophosphate (PRPP) are utilized by phosphoribosyl transferase enzymes to which HGprt belongs to catalyze its reaction. Two of the similar reactions are catalyzed by HGprt during the recycling of purines. One of these reactions includes the pyrophosphorylation of hypoxanthine into inosine monophosphate, while the second one includes the pyrophosphorylation of guanine directly into GMP (Fig. 2). The HGprt catalyzed reaction proceeds via an ordered mechanism, for the sake of subsequent purine binding a conformational change takes place when PRPP binds, this follows the release of nucleotide and pyrophosphate (Harris and Hirschhorn., 1976; Nyhan., 2000).

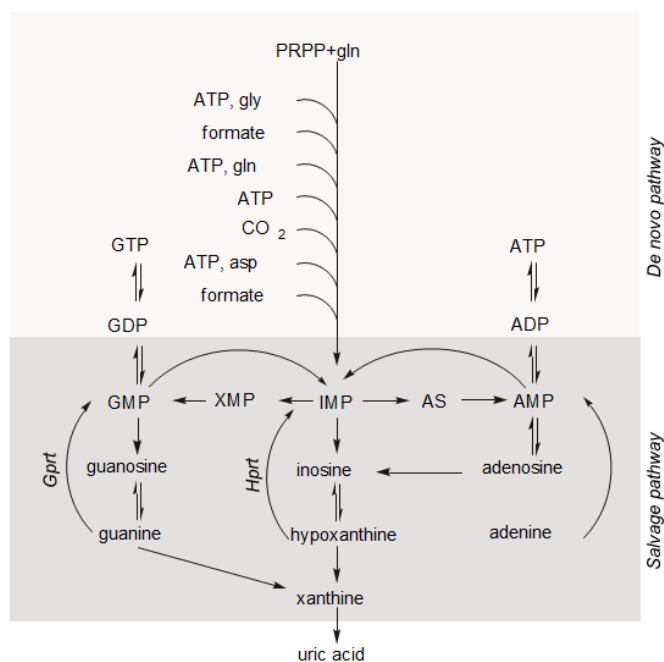


Figure 2. Purine Metabolism

Epidemiology

Suppressed X-linked characteristics are known to be involved in the inheritance of HPRT deficiency. Thus, affected patients are generally males while women are generally known to be asymptomatic carriers. In the literature, due to different molecular mechanisms, five women with Lesch-Nyhan syndrome have been explained. 1/380,000 live births are reported in Canada and 1/235,000 live births in Spain (Garcia *et al.*, 2001).

Clinical Description

No abnormality of any kind is seen in patients with such disease at the time of their birth. The disease shows one of the initial symptoms such as the formation of orange crystals in the diapers also known as crystalluria which is due to the hindrance of the urinary pathway. There are many other types which also involves repeated vomiting with acidosis or renal failure along with some other forms where infants take more than usual in the development of their sitting head support mechanisms with hypotonia and athetoid fluctuations. Within 3 to 6 months, psychomotor delay, if present becomes evident. The biting of lips or chewing of fingers appear as soon as they develop teeth causing selfmutilation. Precisely, symptoms concerning overproduction of uric acid, hematological disturbances and neurological manifestations are seen to occur.

Renal and articular symptoms relating to hyperuricemia: All HPRT-deficient patients exhibit such symptoms (orange crystal formation in the diapers; crytalluria and juvenile arthritis). These symptoms are independent of the severity of the enzyme defect (Nyhan., 2000).

Neurological symptoms: Neurological symptoms may differ in HPRT-deficient deviant. These symptoms depend on how much of the enzyme is present which further describes whether a patient is completely or partially dependent on other for daily life activities. The classification of HPRT deficiency is divided in three classes which depend on the severity of the neurological expression affecting the motor sphere, cognitive and behavioural aspects.

Motor disorder, the best classification of motor syndrome of complete HPRT insufficiency is severe action dystonia, superimposed on a baseline hypotonia. In this case the patients cannot walk or cannot even stand up properly and hence most of them are confined to wheelchair. Cognitive impairment, complete HPRT-deficient patients show very less to average level of mental retardation including disorders where patients are attention deficit. However, they do show non verbal intelligence. Non complete HPRT deficient patients show different varying degrees of mental retardation where patients show different levels of attention deficit while they exhibit normal intelligence.

Compulsive self-injurious behavior, only patients with complete enzyme defect show such behavior. It includes biting of lips, tongue or fingers. Friends and family may experience aggressive behavior from the patients. The patients might get out of control and start sitting and using abusive language against them. This kind of self-mutilation may aggravate by psychological stress and start between the age of 2 and 16 years.

Classifications

The classification of HPRT deficiency is depends on the degree of defect of the enzyme and the complexity of the neurological indication and the patients are divided into four groups: Group 1: normal growth without neurological signs, Group 2: not very serious/mild neurological signs, Group 3: severe neurological signs and Group 4: classic Lesch-Nyhan disease.

Aetiology

Uric acid overproduction: There are many mechanism which can identify excess amount of uric acid in lack of HPRT. In HPRT inosine monophosphate and guanosine monophosphate produced by the reduction of purine bases hypoxanthine and guanine correspondingly. In this reduction reaction of purine bases 5'-phosphoribosyl-1-pyrophosphate (PRPP) used as co-substrate. Due to fault in HPRT its substrate accumulates guanine and hypoxanthine and then it is transformed into uric acid by the action of xanthine oxidase. PRPP amidotransferase has dual nature increase in its availability causes synthesis of purine nucleotides and decrease in its availability causes feedback inhibition in synthesis of inosine monophosphate and guanosine monophosphate. Due to increase production of purine nucleotide overproduction of uric acid causes in HPRT deficiency. Purine overproduction occurs due to increase in level of APRT (Puig., 2007).

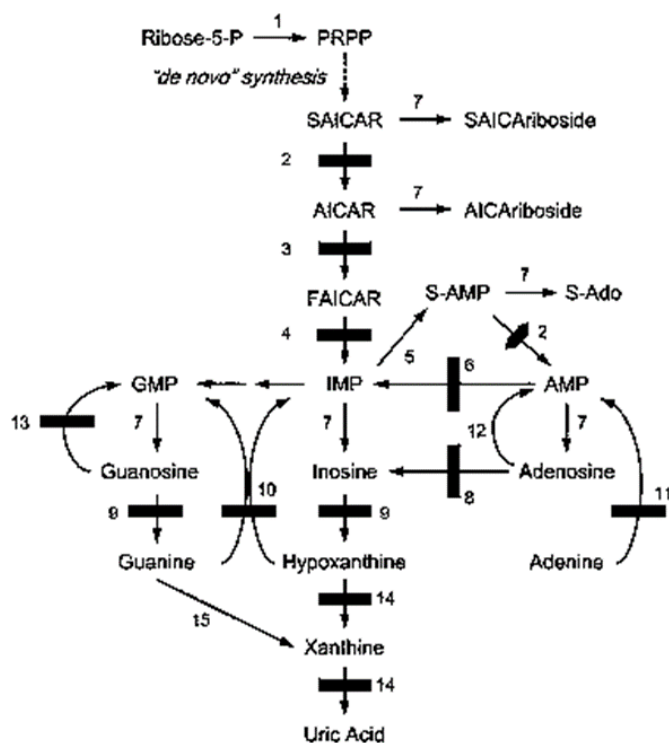


Figure 3. Overproduction of uric acid

Pathophysiology of neurological symptoms: Pathophysiology of behavioral and neurological systems are not clear. Patients of Lesch Nyhan syndrome do not have any clear morphological abnormalities. In Lesch

Nyhan syndrome neurotransmitters of brain loses their functions. In brain function of dopamine secreting transmitters decreases whereas secretion of serotonin and 5-hydroxyindolacetic increases. Dopamine metabolite homovanillic acid level also decreases while xanthine and hypoxanthine concentrations increase. We have discovered through positron-emission tomography that dopaminergic system of brain greatly depressed in Lesch Nyhan syndrome. Animal model was also used for finding the details of Lesch Nyhan syndrome. Breese developed a pharmacological rat model which describes that due to dopamine deficiency self-injurious level increases. After this experiment new born were treated with 6-hydroxydopamine, and due to its introduction catecholamine-containing neurons destroys. Unluckily, HPRT-insufficient knockout mice did not show neurological changes but they clearly show the dopamine reduction in them. Other than dopamine serotonin and adenosine are also involve in Lesch Nyhan syndrome. Among all these conditions overproduction of hypoxanthine is most dominant. Due to its overproduction Na^+ , K^+ and ATP's activity greatly influenced (Hoefnagel., 1965; Puig., 2007).

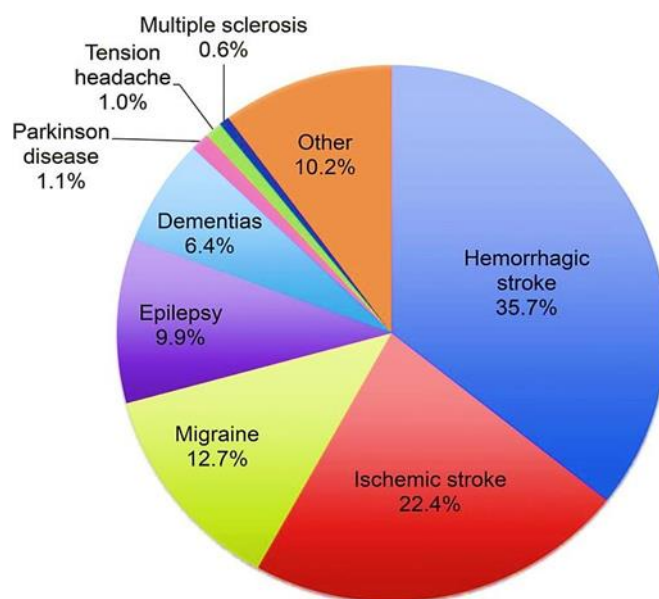


Figure 4. Neurological disorders in human

Treatment

Uric acid overproduction: Overproduction of uric acid can be regulated with the xanthine oxidase inhibitor allopurinol which inhibits the change of xanthine and

hypoxanthine into uric acid. The dose of allopurinol range from 50-600 mg/day. The treatment of allopurinol causes the serum urate and uric acid levels to reduce and thus prevents uric acid crystalluria, nephrolithiasis, gouty arthritis and tophi. Usually renal function remains steady or improves with therapy. In patients with HPRT deficiency, allopurinol is commonly riskless for therapy of uric acid excess quantity.

Motor syndrome: Physical rehabilitation, which includes management of dysarthria and dysphagia, appropriate walking aids, use of special devices for the hand control of objects, and a programme of posture management to prevent disabilities suggested.

Behavioural manifestations: Management of self-harmful attitude can be aided by a mixture of physical restraints, attitude and clinical therapies e.g. use of elbow restraints permit hand use without the chance of finger biting while use of dental guards prevent cheek biting. Stress stimulates such attitude (Anderson and Autism., 1994). Thus, tensions should be prohibited (Figure 3)



Figure 4. Management of self-injurious behavior

Prognosis

After allopurinol treatment, renal function can be established and survival chances of patient increases. Patients of Lesch-Nyhan syndrome cannot move on their feet but they required a wheelchair for moving from one place to other. In such cases patient can be died due to pneumonia and other infections but in most cases sudden

death occurred. This is a respiratory disorder (Puig., 2007).

Phenotypic spectrum of Lesch-Nyhan disease and its attenuated variants

Spectrum of clinical manifestation: Due to secretion of LND mental retardation along with emerging muscle structure occur in first year of life. These problems are very dangerous from 4 to 6 years of life but after the passage of time these problems become stable. Patient of this disease have problem of self-biting and self-hitting. After late teenage these behaviors delayed. Excess quantity of uric acid is common in urine and can be estimated by hyper-uricemia. The quantity of uric acid in these patients is 5 to 10 times more than a healthy person. There are many phenotypes of LND. Among which classic LND is the most dangerous phenotype. There are some physical changes in which patient may appear healthy but they have muscle disability which can be severe but also can be minor in many cases. They also hurt from excess quantity of uric acid. Those physical changes which are mildest have no physical and brain disabilities but overproduction of uric acid also occur in this phenotype. Classic phenotypes can easily diagnosed but milder are tough to diagnose. Classic phenotypes have characteristic symptoms and can easily be identified. All phenotypes have excess quantity of uric acid due to hypoxanthine-guanine phosphoribosyltransferase (HPRT) enzyme lacking. These diseases are common in adults. Kelley-Seegmiller syndrome resembles with Lesch-Nyhan syndrome completely (Rong., 2014)

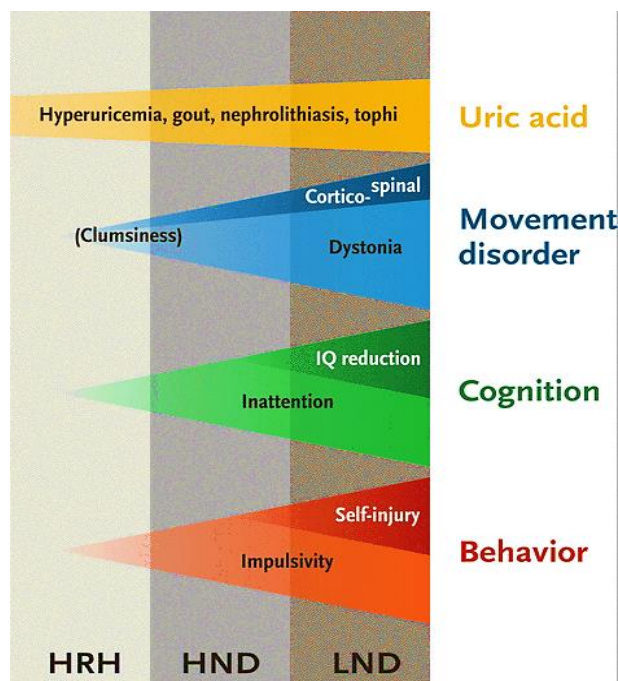


Figure 5. Phenotypic spectrum of Lesch Nyhan syndrome

Molecular and metabolic basis : At X chromosome no 22 a gene HPRT present when it is become defected LND occur. This is an X-linked suppress trait so it is common in men but females will have this disorder if both X chromosomes are defected. These are hetrogenous defects of gene in LND variants. Almost 400 mutations occur in it which involves point mutation, deletions, splicing mutations, insertions, frame shift mutations and many others. Mutations of null enzyme functions cause most complex type of classic LND while changes of residual function cause attenuated viruses. Overproduction of uric acid causes purine salvage, purine synthesis and purine degradation. De novo synthesis occurs in large steps with utilization of large amount of energy. 10 consecutive steps occur and inosine monophosphate (IMP) formed from phosphoribosyl pyrophosphate (PRPP) and also involvement of hydrogen carbonate, aspartic acid, glutamine and formate occur in this step. In this reaction 6 ATP molecules are utilized and 1 IMP formed. PRPP involved in pyrimidine and purine synthesis. De novo synthesis involve the use of enzyme amidophosphoribosyltransferase which catalyzed and PRPP production starts its increased production is inhibited by IMP, GMP and AMP. Purine recycling takes place in human body and its recycling is catalyzed by the use of three enzymes which are APRT, HPRT and adenosine kinase. APRT which has been formed in

cell 90% is recycled rather than excreting out of the body after degradation. Hypoxanthine-guanine ribosyltransferase recycles guanine into GMP and hypoxanthine into IMP. HPRT and APRT both are same in their structures and both of them used PRPP as a co-substrate in their recycling reactions. Animals and plants product also produce purine on their digestion. Purine circulated through blood transfer into other tissues for use. Last thing of purine metabolism in humans and other primates is uric acid while in other mammals uric acid changed into uricase by the degrading action of allantoin. Due to PRPP over activity and HPRT deficiency overproduction of uric acid takes place (Becker *et al.*, 1995; William., 2014).

Mechanism responsible for gout: Gout is a disease of joints. It involves renal clearing of urate, metabolic homeostasis and deffence arrangement. Main cause of gout is monosodium urate. It can causes hyperuricemia which is a result of uric acid overproduction or its inefficient excretion from kidney. Increase amount of uric acid is excreted by urinary uric acid but in patients of gout this phenomenon is reduced. Gout occurs due to production of uric acid which causes hyperuricemia and hyperuricosuria. These defects occur by birth due to lack of HPRT, PRPP overproduction and Glucose 6-phosphatase dehydrogenase deficiency (Von Gierke disease). When quantity of uric acid exceeds from normal level in tissues then monosodium urate crystals produced which causes inflammation in joints. Inflammation can be decreased or removed by removal of crystals through phagocytes and anti-inflammatory cytokines. This type of inflammation occurs in cold areas of body such as feet and hands but they can also present in soft bone of ears (Kelley *et al.*, 1969).

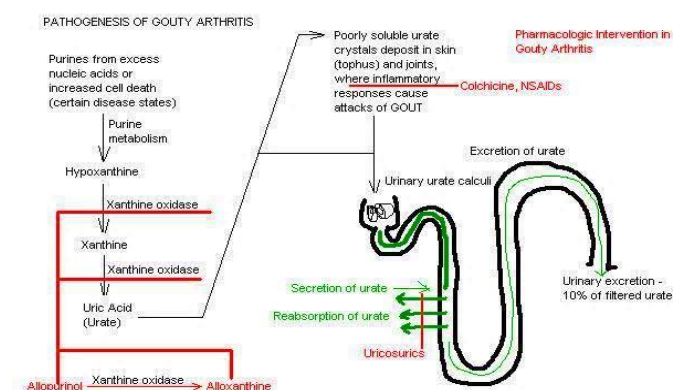


Figure 6. Pathogenesis of Gouty Arthritis

Treatment: The best treatment of uric acid excess quantity is inhibition of xanthine and hypoxanthine transformation into uric acid by using xanthine oxidase inhibitor. Uricosuric is not feasible for this treatment because it can cause over storage of uric acid in kidneys and urogenital system. Allopurinol is highly recommended for this treatment because it does not cause any type of damage (Rosenbloom *et al.*, 1968). Allopurinol provided on daily basis. At start dose is 5 to 10 mg/kg daily then with the passage of time dose quantity increases to 50 to 600 mg/kg daily. Due to this treatment 50% reduction occurs in serum urate and 74% less quantity occur in uric acid. It also increases xanthine inhibition from 5 to 10 folds. Nucleotide concentration also increases in this mechanism which causes de novo purine synthesis. Stone formation also occurs due to uric acid. Then these stones are tested for checking either they composed of xanthine, hypoxanthine or uric acid. This mechanism is hydrated well to avoid crystal formation. Uric acid is quite weak acid has pKa value of 5.75 and PH 7.40. 98% of uric acid present in ionized form in extracellular cells. Monosodium solubility is 18 times greater than uric acid. This solubility change give PH of 6 to urine. pKa value of xanthine is 7.4. solubility of xanthine is 5mg/dL at a PH of 5 while its solubility is 13 mg/dL at a PH of 7. Due to PH changes xanthine stone solubility can also be changed. Xanthine stones are more complicated to soluble rather than uric acid therefore we use allopurinol dose to sustain acid/creatinin ratio lower than 1. Febuxostat is a potent inhibitor used for this process (Rasko and Downes., 1995).

Genotypic and phenotypic spectrum in attenuated variants of Lesch-Nyhan disease

Spectrum of clinical phenotypes: Neurobehavioral disability cause severe problem in motor neurons. Mental disability also occurs in this disease but severe mental retardation does not occur. Mildest phenotype only includes uric acid overproduction. Patients of this disease have HGprt-related hyperuricemia (HRH). Among complex and mild physical changes of LND there is a neurological spectrum called HGprt-related neurological dysfunction (HND). HND victims have excess quantity of uric acid aside with mental retardation but they do not have self harmful attitude like LND patients. They are less severe in symptoms than LND

patients. Patients are divided into three types. Mildest phenotype is very rare only 8.5% cases have it while 75% have LND and 12.4% have intermediate phenotype. Gout is rarely occurs under 15 years of age but mostly it occurs after 20 years. Initial problems are acute renal failure (Rosa and Torres., 2014).

Genotype-phenotype correlations and descriptions:

LND have several clinical problems which involves uric acid excess quantity, motor dysfunction, neurocognitive paralyzes and attitude related crisis including self-injury. It also include mental retardation along with motor neurons disability. Mildest phenotype only includes uric acid overproduction. Patients of this disease have HGprt-related hyperuricemia (HRH). Among complex and mild physical changes of LND there is a neurological spectrum called HGprt-related neurological dysfunction (HND). HND patients have excess quantity of uric acid aside with mental retardation but they do not have self-harmful attitude like LND patients. They are less severe in symptoms than LND patients. Patients are divided into three types. Mildest phenotype is very rare only 8.5% cases have it while 75% have LND and 12.4% have intermediate phenotype. Gout is rarely occurs under 15 years of age but mostly it occurs after 20 years. Initial problems are acute renal failure (Rong., 2014).

Biological basis for neurobehavioral abnormalities:

These problems are not only due to over production of uric acid but it is direct effect of HGprt deficiency in brain during its development (Becker *et al.*, 1995). Ganglion system of brain involved in dopamine production is very vulnerable. Other regions of brain also effected including cerebral cortex. HRH patients do not have any neurological disorder. HGprt activity in it is less severe but it also cause serious effect on brain. MRI study of these diseases showed that HND and HRH are less severe than LND (Harris and Hirschhorn., 1976).

Treatment: LND has several disabilities and problems including overproduction of uric acid, motor dysfunction, neurological and behavioral disorders. It also includes severe motor neurons disability. . Uricosuric is not feasible for this treatment because it can cause over storage of uric acid in kidneys and urogenital system. Allopurinol is highly recommended for this treatment because it does not cause any type of damage.

Allopurinol provided on daily basis. At start dose is 5 to 10 mg/kg daily then with the passage of time dose quantity increases to 50 to 600 mg/kg daily. Due to this treatment 50% reduction occurs in serum urate and 74% low quantity occur in uric acid. It also increases xanthine inhibition from 5 to 10 folds. Nucleotide concentration also increases in this mechanism which causes de novo purine synthesis. Stone formation also occurs due to uric acid. Then these stones are tested for checking either they composed of xanthine, hypoxanthine or uric acid. This mechanism is hydrated well to avoid crystal formation. Uric acid is quite weak acid has pKa value of 5.75 and PH 7.40. 98% of uric acid present in ionized form in extracellular cells. Monosodium solubility is 18 times greater than uric acid. This solubility changes give PH of 6 to urine. pKa value of xanthine is 7.4. solubility of xanthine is 5mg/dL at a PH of 5 while its solubility is 13 mg/dL at a PH of 7. Due to PH changes xanthine stone solubility can also be changed. Xanthine stones are more complex to soluble rather than uric acid therefore we use allopurinol dose to sustain acid/creatinin ratio lower than 1 (Hoefnagel *et al.*, 1965). Febuxostat is a potent inhibitor used for this process. Mildest phenotype only includes uric acid overproduction. Patients of this disease have HGprt-related hyperuricemia (HRH). Among complex and mild physical changes of LND there is a neurological spectrum called HGprt-related neurological dysfunction (HND). HND victims have excess quantity of uric acid aside with mental retardation but they do not have self-harmful attitude like LND patients. They are less severe in symptoms than LND patients. Patients are divided into three types. Mildest phenotype is very rare only 8.5% cases have it while 75% have LND and 12.4% have intermediate phenotype. Gout is rarely occurs under 15 years of age but mostly it occurs after 20 years. Initial problems are acute renal failure (Crawhall *et al.*, 1972; Olson *et al.*, 2000; Torres *et al.*, 2014).

II. CONCLUSION

HGprt enzyme deficiency causes LND attenuated variants. These victims have excess quantity of uric acid in their body and causes gout arthritis. Patients having classic phenotypes are self-injurious in nature and have mental disability. In gout arthritis neurobehavioral disability causes LND variants. Allopurinol helps

greatly in treatment and reduces the risk of mental disability along with gout arthritis.

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