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Research Article www.enlivenarchive.org Enliven: Journal of Genetic, Molecular and Cellular Biology

ISSN: 2379-5700

Deferiprone Related Bone Disease may be related to Associated Gilbert Syndrome

Nupur Parakh*, Puneet Sahi, and Jagdish Chandra

Division of Hematology, Department of Pediatrics, Kalawati Saran Children's Hospital and Lady Hardinge Medical College, New Delhi, India

*Corresponding author: Nupur Parakh, Division of Hematology, Department of Pediatrics, Kalawati Saran Children's Hospital and Lady Hardinge Medical College, New Delhi, India, Email: drnupurparakh@gmail.com

Received Date: 09th August 2022
Accepted Date: 06th October 2022
Published Date: 20th October 2022

Citation: Parakh N, Sahi P, Chandra J. Deferiprone Related Bone Disease may be related to Associated Gilbert Syndrome. Enliven: J Genet Mol Cell Biol. 2022; 10(3): 003.

Abstract

Gilbert Syndrome, is a benign condition characterized by persistent indirect hyperbilirubinemia due to reduced UDP-glucuronyltransferase enzyme activity. Its coexistence with other clinical disorders has important clinical and pharmacological implications. GS is known to coexist with many hemolytic conditions and may lead to diagnostic difficulty and also increased incidence of gallstone. UGT1A1 gene has been shown to be involved in the conjugation of various physiologically important endogenous and exogenous compounds, so individuals with Gilbert mutation (the variant allele UGT1A1*28) have an increased risk of toxicity of various drugs and endogenous compounds like irinotecan, steroid hormones, implicated in various human carcinoma like colorectal and breast carcinoma. Deferiprone (DFP) is an orally available chelator used in the management iron-overload in patients with Thalassemia Major (TM). In this study, fifteen out of 275 patients with TM, had a deferiprone-induced joint deformity. Among these fifteen patients with joint deformity, eleven patients (four patients were homozygous for TA 7 repeats and seven were heterozygous for TA7 repeats) had associated gilbert mutation. Therefore, we hypothesize that patients of TM who had underlying Gilbert mutation might have decreased enzymatic activity of UGTIA6, which metabolizes the DFP, leading to more prominent adverse effects related to DFP.

Keywords: Gilbert Syndrome; Deferiprone; Bone deformity

Introduction

People with Gilbert's Syndrome (G.S) have mild, chronic indirect hyperbilirubinemia in the absence of liver disease or any evidence of hemolysis [1,2]. This benign non-progressive condition does not require any treatment or any long-term medical attention. However, its coexistence with other clinical disorders has important clinical and pharmacological implications.

Bosma et al found that patients with homozygous GS have two extra bases (TA) in the TATAA element of the 5' promoter region of the UGTIAI gene which leads to reduced expression of the reporter gene and reduced UDP-glucuronyltransferase enzyme activity and higher serum bilirubin than the normal subjects [3].

GS is known to coexist with many hematological conditions like Thalassemia major(TM)/intermedia(TI)/ Trait, G-6-PD deficiency, Sickle Cell Disease (SCD), Pyruvate Kinase Deficiency, Congenital Dyserythropoeitic Anemia(CDA), and Hereditary Spherocytosis (HS)[4-10].

Co inheritance of GS with hemolytic conditions may lead to diagnostic difficulty and also increased indirect hyperbilirubinemia. Significantly raised incidence of gallstones has also been reported in GS co inheritance than the primary disease in patients with SCD, CDA, and HS [7,9,10].

The presence of GS mutation has various pharmacological implications, as UDP-glucuronosyl transferases (UGTs) are involved in the metabolism of various drugs. UGT1A1 gene has been shown to be involved in the conjugation of various physiologically important endogenous and exogenous compounds including clinical drugs such as acetaminophen, entacapone (3-O-glucuronidation), SN-38, etoposide, and morphine (3-O glucuronidation) [11-14]. The individuals with Gilbert mutation (the variant allele UGT1A1*28) have an increased risk of toxicity of irinotecan, a cytotoxic drug commonly used for the treatment of colon cancer [15].

Deferiprone (DFP) is an orally administered iron chelator that is commonly used in patients with TM. Commonly reported side effects of DFP therapy include agranulocytosis, arthropathy, and deranged liver function test [16,17]. Recently authors have described distal ulnar changes in Children with TM who are on long-term DFP therapy [18,19].

Assuming that reduced UDP glucronyltransferase enzyme activity in patients with Gilbert mutation (UGTIA1*28), might have some effect on the metabolism of DFP which is also metabolized by the same enzyme but with a different isoform of UGT1 that is UGTIA6, we evaluated the GS mutation status of all patients with TM on DFP therapy, who had DFP induced ulnar or another joint deformity.

Material and Methods

It was a retrospective observational study conducted at the Thalassemia Day Care Centre, a tertiary care center, in New Delhi, India. Children with TM who were on DFP therapy and were found to have either ulnar, elbow, hip, or knee deformity either clinically and or radiologically were included in the study after informed consent from the parents. All these patients were on regular transfusion therapy since infancy and were receiving monthly packed red cells transfusions to maintain pre-transfusion hemoglobin of 95-100g/L. They were prescribed DFP for iron chelation since 2- 4 years at a dose of 75 mg/kg. The children on DFP therapy who had restricted joint mobility or any visible joint deformity were identified during the regular clinical visits. The liver function tests including Serum bilirubin (both total and indirect), AST, ALT, HIV serology and viral marker including HbsAg and Anti HCV were assessed. Reticulocyte counts were also assessed to rule out hemolysis as the cause of indirect hyperbilirubinemia.

The study was approved by the ethics committee of our institution. GS mutation analysis was done using gene sequencing at TATA box mutation. (Technique- Sanger Sequencing. Genomic DNA extracted from the peripheral and TATA Box region identified following the Polymerase Chain reaction, amplicon collected and sent for Sanger sequencing for the number of TA repeats.

Statistical Methods

Baseline variables were analyzed by descriptive statistics. Quantitative variables were described in the form of range, mean, and standard deviation (SD).

Results

Two hundred and seventy-five patients with TM were on regular follow-up at Thalassemia Day Care Center. Fifteen patients with TM who were on DFP therapy for long and were having DFP-induced joint arthropathy and deformity of the joints were evaluated for the gilbert mutations.

Patients Characteristics

The mean age of the subjects was years 14.73± 3.44 years (Range: 6-18 years). All patients were nonreactive for Hepatitis B, Hepatitis C, and HIV. The mean duration of DFP chelation prior to enrollment was 10.86± 2.71 years (range: 6.5 years-13.8 years). DFP was administered as monotherapy in all these patients. The mean administered dosages of DFP was 87.73± 6.44 mg/kg/d. The mean serum indirect bilirubin, ALT and AST were 1.74±1.07 mg/dl, 26.93 ± 4.32 U/L and 28.67 ± 3.83 U/L respectively, (Table 1). The mean reticulocyte count was 0.76± 0.19 in this study population. Five out of these fifteen patients had arthralgia (knee joint arthralgia in 2 patients and two had elbow joint pain and one patient had hip joint pain). Three patients had restricted knee joint involvement. Nine patients had a painless ulnar deformity, one had painless knee joint restricted mobility and one had painful restricted movement of the hip joint. Out of 15 patients, 9 had wrist deformity (both radiologically and clinically). Two patients had elbow deformity (both radiological and clinical) and three patients had restricted movement of knee joint with one having radiological evidence of knee joint. One patient had a hip joint deformity. Four (26.67%) patients were homozygous and 7 (46.67 %) patients were heterozygous for (TA 7 repeats) for GS mutation. In four patients (26.67%) GS mutations were not identified. Patients who were homozygous or heterozygous for GS mutation had mean indirect hyperbilirubinemia 3.0±1.0 mg/dl and 1.28±0.62 mg/dl respectively. In those without GS mutation, serum mean indirect bilirubin level was within normal limit (Table 2).

Table 1. Baseline Patient Characteristics:

Variables	Mean±SD
Age (yr) Mean±SD	14.73± 3.44
Sex Male n (%) Female	80 (12/15) 20 (3/15)
Pretransfusion Hb(g/L) Mean ± SD	93.93± 4.2
Annual Transfusion Requirement (mL/kg/yr) Mean ±SD	140.06±12.97
Serum ferritin (µg/L)	3181.73± 1335.87
ALT (U/L) Mean ± SD	26.93±4.32
AST(U/L) Mean ± SD	28.67±3.83
S. Bilirubin(mg/dl) (indirect) Mean ± SD	1.74 ± 1.07
Mean Reticulocyte count	0.76± 0.19

Table 2. Serum Mean Indirect Bilirubin Level

S.NO	years	Sex	Gilbert mutation	Clinical deformity	Radiological deformity	S. Bilirubin (Indirect) mg/dl	Mean S. Bilirubin (mg/dl)
1.	14.25	M	TA6/TA6	ulnar deformity	Yes	0.5-1.0	0.75
2.	15	F	TA6/TA7	ulnar deformity	Yes	1.0-1.5	1.25
3.	14	F	TA6/TA7	Elbow deformity	Yes	0.5-1.0	0.75
4.	15	M	TA6/TA7	ulnar deformity	Yes	1.1-1.3	1.2
5.	17.75	M	TA6/TA7	ulnar deformity	Yes	1.5-2.5	2
6.	14.75	M	TA7/TA7	ulnar deformity	Yes	4.0-5.0	4.5
7.	14	F	TA6/TA6	ulnar deformity	Yes	0.8-1.0	0.9
8.	18	M	TA6/TA7	ulnar deformity	Yes	0.5-1.0	0.75
9.	14	M	TA6/TA6	ulnar deformity	Yes	2.0-3.0	2.5
10.	15	M	TA7/TA7	elbow deformity	Yes	2.0-3.0	2.5
11.	7.75	M	TA6/TA7	knee deformity	No	2-2.5	2.25
12.	6	M	TA6/TA7	knee deformity	No	0.5-1.0	0.75
13.	14	M	TA7/TA7	ulnar deformity	Yes	2.0-3.0	2.5
14.	15	M	TA7/TA7	Knee deformity	Yes	2.0-3.0	2.5
15.	13	M	TA6/TA6	Hip deformity	Yes	0.5-1.0	0.75

Discussion

GS described in 1901 by Gilbert and Lereboulet, is characterized by fluctuating mild, unconjugated hyperbilirubinemia < 85 µmol/L without overt hemolysis [1]. GS is characterized by reduced levels of UGT1A1 activity to about 25%-30% normal level and is caused by homozygous, or compound heterozygous mutation in the UGT1A1 with autosomal recessive transmission [20]. The genetic basis of GS was first described in 1995 as the presence of the allele UGT1A1*28, characterized by the insertion of TA in the TATAA box (A[TA]7TAA) in the proximal promoter of UGT1A1. The insertion is responsible for the reduction of transcription of UGT1A1 to 20% from normal and for a decrease of hepatic glucuronidation activity by 80% in a homozygous state [3].

Raijmakers et al. studied the correlation between this promoter region polymorphism and in vitro human liver bilirubin UDP-glucuronyl transferase enzyme activity, and found that the median bilirubin UDP-glucuronyl transferase enzyme activity of the 17 subjects with the 6/6 genotype (1565 nmol/g liver/h) was significantly higher than the activity of the 18 subjects with the 6/7 genotype (985 nmol/g liver/h; $p<0.05$) and the six individuals with the 7/7 genotype (749 nmol/g liver/h; $p<0.005$). It was evident from these results that even individuals with heterozygous GS mutations have significantly reduced UDP-glucuronyl transferase enzymatic activity [21].

UDP-glucuronosyl transferases (UGTs) play a critical role in the detoxification of endogenous and exogenous lipophilic substrates, in particular potentially toxic substrates, by conjugating them with glucuronic acid and thereby enhancing the hydrophilicity for excretion in bile and urine [22-24].

Since GS is a common entity in the general population, so the drugs that are metabolized by glucuronidation might show an inter-individual variation in the pharmacokinetic profile in affected individuals and these patients may develop a potentially higher risk for certain drug toxicities.

Patients with metastatic colorectal cancer who were on Irinotecan therapy were at high risk of drug-related toxic adverse effects. Irinotecan is a topoisomerase I inhibitor that interrupts DNA replication in cancer cells [25,26]. The irinotecan prodrug is activated by the enzyme carboxyl esterase to the active metabolite SN-38 (7-ethyl-10-hydroxy camptothecin), which is 100–1000 times more cytotoxic than the parent drug. SN-38 is further catalyzed into an inactive glucuronide derivative, SN-38G by several hepatic and extrahepatic UGT1 enzyme mainly UGT1A1, but others (UGT1A 6, 7, 9, and 10) also have some role [27]. A decrease in the level of functional UGT1A1 enzyme reduces a person's ability to metabolize SN-38 to an inactive form and increases the risk for adverse reactions [28]. Similarly, GS subjects may be more susceptible to the adverse effects of some drugs metabolised by UGT1A1, such as indinavir, and atazanavir [29-33].

Guillemette et al., reported an association between the UGT1A1 promoter polymorphism and an increased breast cancer risk in premenopausal African-Americans due to altered activity towards steroid hormones such as estradiol, as a result of this polymorphism [34]. In addition, Bigler et al. demonstrate that UGT1A6 genotypes may modulate the protective effect of aspirin on colon adenoma risk [35].

Chronic transfusion therapy and iron chelation are the two pillar in the management of patients with β-thalassemia major (TM) especially in the developing country. Deferiprone (DFP) is an orally available chelator that improves compliance and quality of life in these patients. DFP was the most widely used chelator in developing countries over a long period of time before deferasirox became available.

What Led us to Think about the Association of Ulnar Deformity and GS Mutation?

During regular follow up, incidentally one of the patients of TM who had DFP deferiprone-induced joint deformity was also found to have, indirect persistent hyperbilirubinemia with no evidence of hemolysis and normal transaminase levels. Therefore, GS mutation was looked for, and he turned out to be homozygous for TA7 repeats. So assuming that reduced enzyme activity in the GS mutation (UGTIA1*28) might have some effect on the metabolism of deferiprone, we tried to evaluate the status of other patients who had DFP deferiprone ulnar or other joint deformity. To our surprise out of 15 patients who had clinical arthropathy 4 patients were homozygous for TA 7 repeats and 7 were heterozygous for TA7 repeats.

We searched the literature for the association of GS mutation and the metabolism of DFP, as the results in our observation were suggesting that the risk of DFP induced arthropathy especially (ulnar) was high in patients with GS mutation either in homo or heterozygous gilbert state. However, in literature search we found that the enzyme involved in DFP metabolism is UGTIA6 which is different from that involved in the GS mutation which is UGTIAI*28 [36].

Peters et al. pointed out that a large percentage (87%) of individuals homozygous for the UGT1A1*28 allele, suffering from GS, are also homozygous for the UGT1A6*2 allele, implicating that these individuals may also have abnormalities in the conjugation of various drugs such as coumarins or non-steroidal anti-inflammatory drugs and concluded that approximately 90% of the Caucasian patients with GS, in addition to the reduced B-UGT activity, may have abnormalities in the glucuronidation of several drugs such as aspirin, and coumarin- and dopamine-derivatives, due to the combined UGT1A1*28 and UGT1A6*2 genotypes [37].

Similarly, frequent co-occurrence of the TATA box mutation associated with GS(UGT1A1*28) with other polymorphisms of the UDP-glucuronosyltransferase-1 locus (UGT1A6*2 and UGT1A7*3) in Caucasians and Egyptians have been reported by Kohle et al by fluorescence resonance energy transfer techniques [38].

Lampe et al studied the co-occurrence of polymorphisms in UGT1A1 and UGT1A6 in 245 healthy men and women and found that 8% were homozygous variants for both UGT1 polymorphisms and 43% had at least one variant allele for both UGT1A1*28 and UGT1A6*2. These highly prevalent polymorphisms, which result in modified expression and activity of UGTs, may influence susceptibility to cancers associated with altered metabolism of endogenous and xenobiotic compounds [39].

Therefore assuming the co-occurrence of polymorphisms in UGT1A1 and UGT1A6 in our patients with TM and gilbert syndrome (homozygous or heterozygous), we generate a hypothesis that these patients were more prone to DFP induced joint deformity, due to decreased metabolism of this drug in TM patients with Gilbert mutation.

This study shows that 11 of the 15 patients (73.3 %) who suffered from DFP-induced bone/ joint deformities, had homozygous or heterozygous GS mutation. Although we have not been able to study the GS mutation typically incriminated in DFP metabolism, but as suggested by previous studies on co-inheritance of both mutations, a causal association of GS mutation with DFP induced deformities is hypothesised and deserves further study.

Disclosures

The authors have no conflict of interest or sources of funding to declare.

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