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GILBERT'S SYNDROME-CASE REPORT

Paediatrics

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ABSTRACT

Gilbert's syndrome is benign,inherited condition that runs in the families,characterized by recurrent but asymptomatic episodes of mild unconjugated hyperbilirubinemia without liver pathology or haemolytic cause.This syndrome is caused due to mutation UGT1A1 gene that decreases the activity of UDP-glucuronosyl transferase1.It is mostly inherited by autosomal recessive pattern and sometimes by autosomal dominant pattern depends on type of mutation.The presence of gilberts genotype,make other pathological causes of jaundice less likely.Genetic polymorphisms in the TATA box of UDPGT gene can be identified by PCR method.We are reporting a case of 14 year old adolescent female presenting with icterus.On examination except jaundice,clinically all parameters are within normal limits.PCR revealed genetic polymorphism.

KEYWORDS

Gilbert's syndrome,Unconjugated hyperbilirubinemia,UDP-glucuronosyl transferase

INTRODUCTION

Gilbert's syndrome is the benign condition.It is characterised by recurrent intermittent episodes of asymptomatic mild unconjugated hyperbilirubinemia[1].It is presented mostly in the adolescent period.The episodes are mostly caused by intercurrent illness,fasting or due to stress.Almost all the persons having Gilbert's syndrome have decreased level of UDP-glucuronosyl transferase activity that decreases the uptake of bilirubin by the liver and bilirubin conjugation.

Case report

A 14 year old adolescent girl presented with history of yellowish discolouration of skin and eyes of 4 days duration. Urine colour was normal. She had similar episodes in the past with episodes occuring once in 3 months from last 2 years,since she attained her menstrual cycles. The episodes subside on its own. Child was taken to nearby Ayurvedic doctor 1 year back for which she was treated ,but with no resolution of symptoms. Hence child was brought to RLJH for further evaluation.

On physical examination, Vital parameters and anthropometry measures were within normal limits,mild icterus was present, evident in eyes and skin. Systemic examination was normal. Investigations done revealed normal Haemoglobin, total wbc counts,differential wbc counts and platelet count. Reticulocyte count and peripheral blood picture were within normal limits. Liver function tests revealed unconjugated hyperbilirubinemia. Serology done, revealed negative for hepatitis B and hepatitis C. Urine routine, chest radiography and USG abdomen done were also normal.Liver function test done at two distinct intervals revealed unconjugated hyperbilirubinemia {during pharyngitis(TB:IB) is (10.6:8.8) and during menstrual cycle (TB:IB) is (7.4:6.3)}and LFT done inbetween intervals were within normal limits.History of similar complaints were present in the father ie. Episodes of yellowish discolouration of skin and eyes, which started from the age of 14-15 years and observed that episodes frequently occurred during minor illness or fasting. H/o similar episodes of intermittent jaundice was present in the father's maternal grandmother (expired). There is h/o second degree consanguineous marriage in the family.

In view of patient having episodes of intermittent, benign, unconjugated hyperbilirubinemia, according to age of presentation (ie adolescent) and also history of similar complaints in her father and maternal great grandmother and history of second degree consanguineous marriage and also having all the investigations within normal limit, mostly the cause can be inherited. Gilbert syndrome should be taken as a differential diagnosis in such case, as it can cause isolated benign unconjugated hyperbilirubinemia on various occasions, in the absence of any liver pathology or haemolytic cause. Gilbert syndrome which is the best predicted possibilities can be confirmed by PCR, which is a novel and also rapid method to identify genetic polymorphism in the TATA box of UDPGT gene (which is responsible for Gilberts). In the absence of Gilbert genotype, denotes that person may have a pathological cause for their jaundice. However , the presence of gene cannot exclude liver and haemolytic disease, because they can coexist with Gilberts, but one might assume that the presence of Gilberts genotype make other causes less likely.

TESTS TO CONFIRM GILBERTS SYNDROME AFTER OBTANING INFORMED CONSENT:

DNA isolation: Three ml of blood each was collected in EDTA vaccutaners from the patient, her father and mother for DNA isolation.Standard salting out method was used to extract DNA from the blood. 7.2ml of dissolved DNA was added to each 25ml PCR reactors.

Molecular analysis: The variant was characterized by PCR using primers in the promoter region of UGT1A1 gene. The amplicon was sequenced on ABI PRISM 3100 Genetic Analyser by Sanger's method and the chromatograms generated were checked or A (TA) 6TAA variation in the promoter region of UGT1A1 gene.

Results: The chromatogram of the patient, the father and mother were checked for the mutation which has shown homozygous for A (TA) 7TAA allele in the promoter region of UGT1A1 gene, that implies that they were likely to be affected with Gilberts syndrome

DISCUSSION

Gilbert syndrome is the hereditary genetic disorder that runs in the families. This was first described by French gastroenterologist Augustin Nicoles Gilbert and his co workers in 1901. Other common names for this syndrome are[8]

1) Familial benign unconjugated hyperbilirubinemia
2) Constitutional liver dysfunction
3) Familial nonhaemolytic non obstructive jaundice
4) Icterus intermittens juvenilis
5) Unconjugated benign bilirubinemia
6) Meulengracht syndrome

Bilirubin is the metabolic end product of heme. Before bilirubin get excreted into the bile, it has to undergo glucuronidation by the enzyme bilirubin-uridine diphosphoglucuronate glucuronosyl transferase (UDPGT). UGT1A1 which is the primary isoform of UDPGT is needed for bilirubin glucuronidation. Gene for UGT1A1 is located on the human chromosome 2. Gilbert syndrome is caused due to mutation of UGT1A1 gene that decreases the activity of UDP-glucuronosyl

transferase[1]. Most common polymorphism is the insertion of TA in the promoter region of UGT1A1 that leads to decrease binding of the TATA binding protein and thus decrease gene activity upto 30%. UGT1A1 is involved in glucuronidation of many other substrates other than bilirubin like environmental toxins, endogenous hormones, drugs, and also aromatic hydrocarbons, which leads to their inactivation. Hence UGT1A1 gene mutation is implicated in cancer risk and predisposed to drug toxicity mainly in cancer chemotherapy and jaundice episodes may aggravate when exposed to the agents. Gilbert's syndrome is mostly inherited by autosomal recessive pattern and sometimes by autosomal dominant pattern depends on the mutation. Ratio of unconjugated to conjugated bilirubin is higher in person with Gilbert syndrome when Compare to other normal individual. As it effects on drug and bilirubin breakdown and because of its genetic inheritance, Gilbert's syndrome can be classified as minor IEM. Several analysis found that there is decreased risk of coronary artery disease in patient with Gilbert syndrome. This beneficial effect is mainly because of bilirubin IXA, which is a potent antioxidant. This has been noticed in the long term data from the Framingh Heart study.

DIAGNOSIS:

1. **PCR:**This is the rapid and novel method of identifying genetic polymorphisms in the the TATA box of UDPGTgene[6]

2. **Thin layer chromathography**:This is also one of the diagnostic test for gilberts syndrome .This test shows increased ratio of bilirubin mono glucuronide to di glucuronide indicating reduced BILIRUBIN-UDPGT activity

3. **Fasting test**: Plasma unconjugated bilirubin rises 2-3 fold within 48 hrs of fast and returns to normal within 24hrs of resuming normal diet .Even though the unconjugated bilirubin increases with fasting in patients with liver or haemolytic disease, the level of rise is less than that of gilbert syndrome

4. **Rifampicin test:** It is a non-invasive test and as reliable as fasting test.After oral administration of 600-900 mg Rifampcin, plasma level of unconjugated hyper bilirubin rises

Factors that predispose to jaundice episodes:

Various factors that predispose to jaundice episodes[8]

1. Illness
2. Infection
3. Starvation or fasting
4. Dehydration
5. Stress
6. Menstruation
7. over excertion
8. Lack of adequate sleep
9. Alcohol intake

Even though Bilirubin levels do not reach to very high degree, but the jaundice can be disturbing. Some may experience fatigue and abdominal discomfort also

Drugs to be avoided if possible

1. Atazanavir and Indinavir used in HIV infection
2. Gemfibrozil that lowers cholesterol
3. Statins
4. Irinotecan, used in treatment of advanced bowel cancers, causes neutropenia and severe diarrhoea in gilberts syndrome patients, as this drug is metabolized by UGT1A1[7]
5. Nilotinib used in treatment of some blood cancers
6. A subset of people with gilbert syndrome may have increased risk of paracetamol toxicity

TREATMENT: As Gilberts syndrome is a benign condition which does not usually cause any health problem, no treatment is required. Even though intermittent episodes of jaundice may reoccur there is no need to bother about it .As this condition does not damage liver, no need for long term follow up or monitoring needed. Expect jaundice, there are no other known complication .Plasma bilirubin level can be normalised by using Phenobarbitone.

Episodes of jaundice can be minimised by avoiding unnecessary drugs, maintaining hygiene to prevent infections and healthy life style

DIET: Even though change in the diet is not necessary, some modification to the diet may be helpful to prevent jaundice episodes[9]

1. Consuming balance diet with fresh fruits and vegetables
2. Do not skip meals
3. Avoid fasting and very low caloric diet
4. Drinking plenty of water to prevent dehydration

Conclusion: Any case of isolated benign unconjugated hyperbilirubinemia on various occasions, without the evidence of liver pathology or haemolysis, GILBERT SYNDROME should be taken for differential diagnosis as it is the common inherited cause for benign unconjugated hyperbilirubinemia,with no other deleterious associations and have excellent prognosis[6]. Patients with gilberts syndrome can lead a complete normal life style with some small dietary and life style modifications to prevent jaundice episodes.

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