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Case report

Non tumoral hyperserotoninaemia responsive to octreotide due to dual polymorphism in UGT1A1 and UGT1A6

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ABSTRACT

Gilbert's syndrome is a common inherited metabolic disorder, caused by genetic aberration in the enzyme UDP-glucuronosyl-transferase 1A1 that leads to reduced glucuronidation of bilirubin. Recent advances in molecular genetics have frequently reported the concurrence of dual genetic polymorphisms in UDP glucuronosyl-transferases 1A6 and 1A1 in patients with Gilbert's syndrome, leading to defective glucuronidation of bilirubin, as well as several other endogenous and exogenous substrates, such as serotonin. We present a case of Gilbert's syndrome with severe persistent hyperserotoninaemia, mimicking carcinoid syndrome, due to dual polymorphisms in UDP-glucuronosyl-transferases 1A1 and 1A6. The patient was treated with a long-acting somatostatin analogue (octreotide) for 8 months, resulting in a significant reduction in serum serotonin levels and immediate relief of the symptomatology, followed by a long-term remission. The frequent occurrence of hyperserotoninaemia in Gilbert's syndrome may contribute, at least partly, to the nonspecific symptomatology commonly seen in these patients and should be promptly evaluated.

Key words: Hyperserotoninaemia, Gilbert's syndrome, Octreotide, UDP-glucuronosyl-transferases, Carcinoid syndrome

INTRODUCTION

Gilbert's syndrome is a common inherited metabolic disorder affecting 9% of the general population.[1] It is associated with decreased activity of the enzyme uridine diphosphate (UDP) glucuronosyl-transferase 1A1, which is located on the endoplasmic reticulum of hepatocytes, leading to deficient glucuronidation of bilirubin and therefore mild hyperbilirubinaemia.[2]

The disease is usually benign and is diagnosed when mild, predominantly, unconjugated hyperbilirubinaemia and jaundice occur under certain physiological or pathological conditions such as fasting, physical or surgical stress, febrile illness and menses or pregnancy, in the absence of liver deficiency or haemolytic diseases.[3,4] Symptomatic patients present

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with nonspecific complaints, such as gastrointestinal discomfort, fatigue, malaise and vasomotor or psychiatric manifestations, which can resolve spontaneously and are, paradoxically, not related to high bilirubin levels.[5,6]

At the molecular level, recently emerging data have established the increased frequency of dual genetic polymorphisms in UDP glucuronosyl-transferases 1A1 and 1A6 in approximately 87% of patients with Gilbert's syndrome, leading to defective glucuronidation not only of bilirubin but of several other endogenous and exogenous substrates, such as serotonin, coumarin and dopamine derivatives.[7,8]

Increased serotonin levels have been reported in patients with Gilbert's syndrome, suggesting a possible explanation for the nonspecific symptoms described in these patients that are commonly attributed to anxiety.[9,10]

We present a case of Gilbert's syndrome and severe persistent hyperserotoninaemia, mimicking carcinoid syndrome, originally treated with the somatostatin analogue octreotide and finally attributed to dual polymorphism in UDP-glucuronosyl-transferases 1A1 and 1A6.

CASE PRESENTATION

A 38-year old white female was referred to the Endocrinology Division complaining of recurrent episodes of gastrointestinal discomfort, including diarrhea and floating, palpitations and night sweats over the last 3 years. The duration and the severity of the episodes were aggravated during the last year. The first episode was reported a few months after pregnancy and lactation. At that time the patient was admitted to the hospital for tachycardia (150-170 b.p.m), abdominal pain, diarrhea, myoclonus, tremor and increased night sweats.

Clinical examination had revealed diffuse abdominal sensitivity with sinus rhythm in ECG and increased blood pressure (180/110 mmHg) without postural variation. Propanolol was successfully used to control the symptoms. According to her medical record, Gilbert's syndrome had been diagnosed in adolescence based on mild hyperbilirubinemia and jaundice during fasting. No genetic analysis was performed at that time to confirm the diagnosis.

Biochemical and hormonal evaluation excluded any common endocrine or metabolic disorder as the underlying cause of her symptoms. Increased serum levels of serotonin and slightly elevated urine 5 indolohydroxylacetic acid (5HIAA) were revealed in repeated blood testing during episodes (Table 1).

Imaging studies

The patient was extensively examined via computed tomography (CT) of the chest, mediastinum, abdomen and pelvis, octreoscan and endo-arterial angiography all of which failed to detect a carcinoid tumor. Due to persistence of the gastrointestinal symptoms related to increased levels of serotonin, we also performed a positron emission tomography

Table 1. Laboratory results performed 3 years after the first reported episode

Parameter	Value	Reference range
Serum		
Sodium	140 mmol/L	134-146 mmol/L
Potassium	3.8 mmol/L	3.4-4.4 mmol/L
Creatinine	86 umol/L	69-113 umol/L
Albumin	43 g/L	37-48 g/L
Bilirubin	**28 umol/L**	4-21 umol/L
CRP	<5mg/L	<10 mg/L
TSH	2.55 μIU/ml	0.35-5.5 μIU/ml
FT4	1.27 ng/dl	0.9-1.8 ng/dl
FT3	2.99 pg/ml	2.3-4.2 pg/ml
E2 (follicular phase)	412 pg/ml	150-500 pg/ml
FSH (follicular phase)	4.45 IU/l	2.5-10.2 IU/l
LH (follicular phase)	5.95 IU/l	1.9-12.5 IU/l
Calcitonin	2.27 pg/ml	<17 pg/ml
Serotonin	**1200 nmol/l**	500-900 nmol/l
Plasma		
Haemoglobin	125 g/L	115-151 g/L
Noradrenaline	385 pg/ml	100-550 pg/ml
Chromogranin A	6 nmol/l	<4 nmol/l
24h Urine		
Metanephrines	335 μg/24h	100-800 μg/24h
Normetanephrines	253 μg/24h	88-444 μg/24h
Serotonin mg/24h	**19 mg/24h**	<2.5 mg/24h
5-HIAA mg/24h	**10 mg/24h**	0-6 mg/24h

with 5-hydroxy-L-tryptophan (5 HTP-PET) which also revealed no signs of a neuroendocrine tumor.

THERAPEUTIC APPROACH

The patient received an anti-serotoninergic agent, sertraline (Zoloft), for 10 days in order to lower serotonin levels, as has been previously described,[12] without any significant improvement. Administration of octreotide (Sandostatin LAR) 20 mg/IM monthly for 8 consecutive months resulted in significant decrease of serum serotonin levels, followed by an immediate improvement in the patient's clinical condition. Octreotide therapy was discontinued when the results of the genetic analysis became available.

GENETIC ANALYSES

The genetic study included UGT1A1 genotyping (Klatovy Biolabs, Czech Republic) and investigation of polymorphisms of exon 1 of the UGT1A6 gene with restriction fragment polymorphism analysis (RFLP) after polymerase chain reaction, as previously described.[7]

The sample was found to be homozygous for the mutation 7/7TA of the UGT1A1 gene in the TATA box of the promoter (UGT1A1*28 genotype). This polymorphism is characterized by the presence of an additional TA repeat in the TATA sequence of the UGT1A1 promoter, i.e. (TA) 7TAA, instead of (TA) 6TAA which results in reduced expression of the enzyme, diagnostic of Gilbert's syndrome.

In addition, the sample was found to be heterozygous for the missence substitutions T181A and R184S in the UGT1A6 gene (UGT1A6*2 genotype). These variant alleles for UGT1A6 are mostly (>98%) in complete linkage disequilibrium (Figure 1).

FOLLOW-UP

Subsequent to two years of follow-up after the last administration of octreotide, the patient remains asymptomatic with serotonin levels within normal range (Figure 2).

DISCUSSION

Dual polymorphisms in the enzymes UGT1A1 and UGT1A6 have previously been reported to occur with high frequency in patients with Gilbert's syndrome.[7-9]

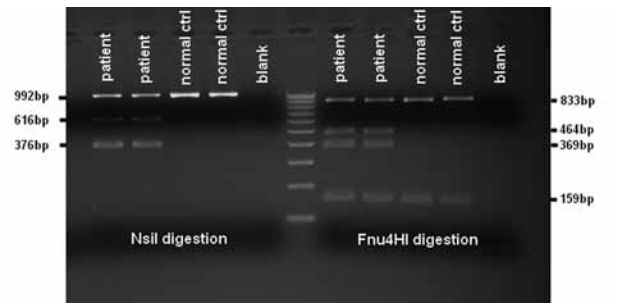

Figure 1. Fragment analysis patterns of PCR products for detection of genetic polymorphisms in UGT1A6. Electrophoresis patterns of PCR fragments after digesting with NsiI for the UGT1A6 T181A polymorphism and after digesting with Fnu4HI for the UGT1A6 R184S polymorphism. Heterozygosity for the variant alleles of the patient is shown (duplicates of a homozygous normal control sample are also included for comparison).

The superfamily of UDP-glucuronosyl-transferases consists of membrane-bound enzymes, located on the endoplasmic reticulum, that catalyze glucuronidation of various endogenous and exogenous compounds.[13,14] The contribution of UGT1A1 to the metabolic pathway of bilirubin and its association with Gilbert's syndrome is well documented but the exact role of the enzyme UGT1A6 has only recently been elucidated.

Peripheral serotonin is produced by the enterochromaffin cells in the gastrointestinal system by its precursor amino-acid tryptophan.[15] Approximately 30% of circulating serotonin is excreted by the urine after glucuronidation, while the rest is oxidized by the enzyme monoamino oxidase (MAO) and aldehyde dehydrogenase in kidney and liver and excreted as 5-hydroxy-indoleacetaldehyde (5IHHA).[16] UGT-1A6 isoform is exclusively responsible for the glucuronidation of serotonin.[13] Three major missence mutations have been identified in the UGT1A6 gene: S7A (19t➔g), T181A (541a➔g) and R184S (552a➔c). The UGT1A6*2 allele (T181A and R184S), which is present in our case, represents more than 30% of identified alleles[13,17-19] and leads to a 30-50% reduced enzyme activity compared with the wild-type allele.[11] However, the presence of the UGT1A6*2 allele may not be enough to explain clinically apparent hyperserotoninaemia.

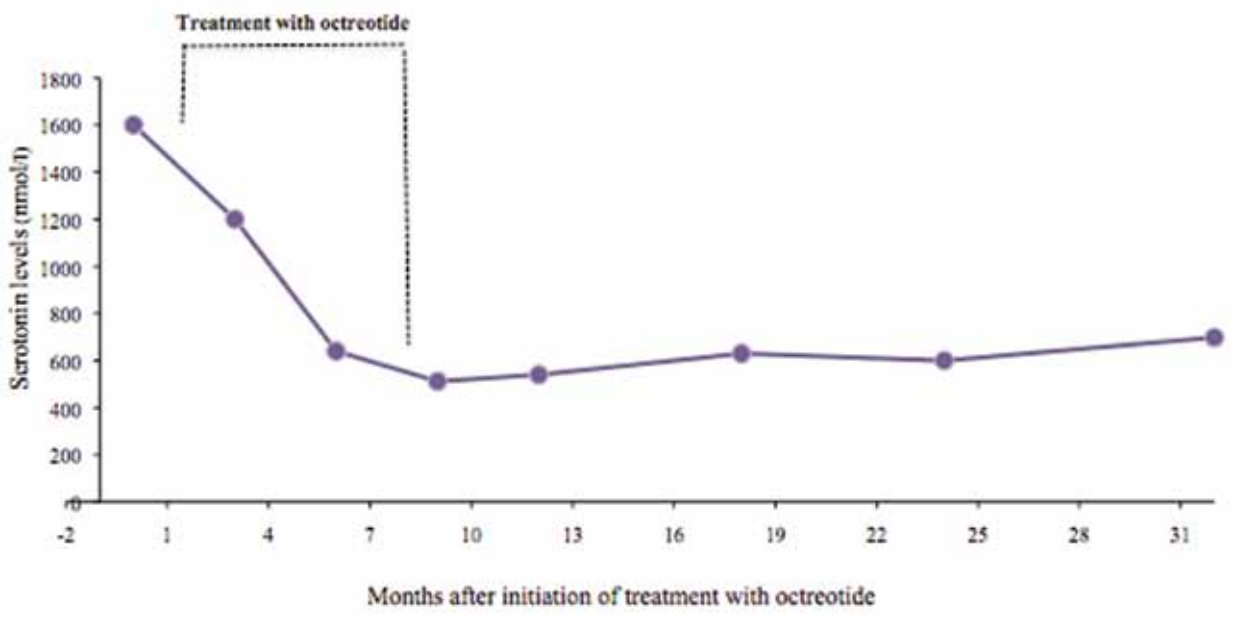

Figure 2. Changes in serum serotonin levels during treatment with octreotide.

UGTs usually form homo- and hetero-oligomers. The heterodimerization of UGT1A1 or UGT1A4 with UGT1A6 increases the Vmax value of serotonin O-glucuronide formation.[20] Therefore, co-existence of the two mutated alleles UGT1A1*28 and UGT1A6*2 in a heterodimer form could further affect enzyme kinetic parameters of the latter, lowering the Vmax/km of serotonin-O-glucuronidation.

A recent study by Lee et al[10] also presented a patient with Gilbert's syndrome and hyperserotoninaemia with dual polymorphisms in the UGT-1A1 and UGT1A6 genes, suggesting a possible link between the molecular genetics and the clinical presentation of this patient. Our case lends further support to this notion, although molecular studies are needed in order to clarify this issue. However, in the above mentioned case, the patient's symptomatology subsided spontaneously after a period of 12 months, consistent with a decline in serum serotonin levels. In our patient, symptomatology persisted for a longer period of time, severely affecting the quality of her life, while anti-serotoninergic agents did not relieve her symptoms.

Somatostatin analogues have been efficiently used in the treatment of neuroendocrine tumors that express somatostatin receptors. Administration of octreotide in our patient significantly improved her clinical condition and increased the duration of the symptom-free period, associated with reduced serum serotonin levels.

Our study suggests that in patients with Gilbert's syndrome and hyperserotoninaemia with non-apparent neuroendocrine tumor, a genetic analysis should be performed, while in cases of persistent hyperserotoninaemia-induced symptomatology treatment with a somatostatin analogue could be considered as an off-label alternative therapeutic approach.

REFERENCES

1. Bosma PJ, Chowdhury JR, Bakker C, et al, 1995 The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med 333: 1171-1175.
2. Hsieh TY, Shiu TY, Huang SM, et al, 2007 Molecular pathogenesis of Gilbert's syndrome: decreased TATA-binding protein binding affinity of UGT1A1 gene promoter. Pharmacogenet Genomics 17: 229-236.
3. Felsher BF, Rickard D, Redeker AG, 1970 The reciprocal relation between caloric intake and the degree of hyperbilirubinemia in Gilbert's syndrome. N Engl J Med 283: 170-172.
4. Barrett PV, 1971 Hyperbilirubinemia of fasting. JAMA 217: 1349-1353.
5. Powell LW, Hemingway E, Billing BH, Sherlock S, 1967

Idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome): A study of 42 families. N Engl J Med 277: 1108-1112.
6. Gitlin N, 1967 The clinical presentation of Gilbert's disease in 26 patients. S Afr Med J 52: 19-20.
7. Peters WH, te Morsche RH, Roelofs HM, 2003 Combined polymorphisms in UDP-glucuronosyl-transferases 1A1 and 1A6: implications for patients with Gilbert`s syndrome. J Hepatol 38: 3-8.
8. Köhle C, Möhrle B, Münzel PA, et al, 2003 Frequent co-occurrence of the TATA box mutation associated with Gilbert's syndrome (UGT1A1*28) with other polymorphisms of the UDP-glucuronosyl-transferase-1 locus (UGT1A6*2 and UGT1A7*3) in Caucasians and Egyptians. Biochem Pharmacol 65: 1521-1527.
9. Borcsiczky D, Szalay F, Tekes K, Tarcali J, Magyar K, Chatel R, 1996 Platelet serotonin (5HT) content is decreased in patients with alcoholic liver cirrhosis, but elevated in Gilbert's syndrome. J Hepatol 25: 781-782.
10. Lee P, Jones G, Seibel MJ, 2007 Dual polymorphisms in UDP-glucuronosyltranferases 1A1 and 1A6: a novel mechanism for hyperserotoninaemia in Gilbert's syndrome mimicking carcinoid syndrome? Eur J Gastroenterol Hepatol 19: 337-340.
11. Lampe JW, Bigler J, Horner NK, Potter JD, 1999 UDP-glucuronosyltransferase (UGT1A1*28 and UGT1A6*2) polymorphisms in Caucasians and Asians: relationships to serum bilirubin concentrations. Pharmacogenetics 9: 341-349.
12. Cheung NW, Earl J, 2001 Monoamine oxidase deficiency: a cause of flushing and attention-deficit/ hyperactivity disorder? Arch Intern Med 161: 2503-2504.
13. Krishnaswamy S, Duan SX, von Moltke LL, Greenblatt DJ, Court MH, 2003 Validation of serotonin (5-hydroxytryptamine) as an in vitro substrate probe for human UDP-glucuronosyltranferase (UGT) 1A6. Drug Metab Dispos 31: 133-139.
14. Bock KW, Kohle C, 2005 UDP-glucuronosyl-transferase 1A6: structural, functional, and regulatory aspects. Methods Enzymol 400: 57-75.
15. Lesurtel M, Soll C, Graf R, Clavien PA, 2008 Role of serotonin in the hepato-gastrointestinal tract: an old molecule for new perspectives. Cell Mol Life Sci 65: 940-952.
16. Bartlet AL, Gilbert FM, 1971 Estimation of urinary 5-hydroxytryptamine-O-glucuronide, a metabolite of endogenous 5-hydroxytryptamine in sheep. Br J Pharmacol 41: 530-539.
17. Krishnaswamy S, Hao Q, Al-Rohaimi A, et al, 2005 UDP-glucuronosyltranferase (UGT) 1A6 Pharmacogenetics: II. Functional Impact of the Three Most Common Nonsynonymous UGT1A6 Polymorphisms (S7A, T181A, and R184S). J Pharmacol Exp Ther 313: 1340-1346.
18. Ciotti M, Marrone A, Potter C, Owens IS, 1997 Genetic polymorphism in the human UGT1A6 (planar phenol) UDP-glucuronosyl-transferase: pharmacological implications. Pharmacogenetics 7: 485-495.
19. Nagar S, Zalatoris JJ, Blanchard RL, 2004 Human UGT1A6 pharmacogenetics: identification of a novel SNP, characterization of allele frequencies and functional analysis of recombinant allozymes in human liver tissue and in cultured cells. Pharmacogenetics 14: 487-499.
20. Fujiwara R, Nakajima M, Yamanaka H, Katoh M, Yokoi T, 2007 Interactions between Human UGT1A1, UGT1A4, and UGT1A6 affect their enzymatic activities. Drug Metab Dispos 35: 1781-1787.