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Gilbert syndrome: case report and review of available diagnostic approaches

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A 16-year old male was admitted with complaints on sore throat, unilateral knee joint pain and general weakness. Pre-operation lab check revealed normal values of all liver tests except of hyperbilirubinemia due to elevated unconjugated bilirubin. Due to persistently normal liver tests, except of unconjugated hyperbilirubinemia, and repetitive episodes of jaundice in a young male with no signs of alcoholic, metabolic and viral liver disease, diagnosis of Gilbert syndrome was made, which was later confirmed by UGT1A1 gene mutations test. Gilbert syndrome is the most prevalent inherited disorder of bilirubin metabolism, affecting 10% of the population. Nonhemolytic unconjugated hyperbilirubinemia, without any effect on prognosis and life expectancy of the patient is the distinctive feature of Gilbert syndrome. Gilbert syndrome is usually diagnosed by exclusion of other more prevalent liver diseases, in difficult diagnostic situations use of UGT1A1 gene mutation is advised.

Key words: Gilbert syndrome, hyperbilirubinemia, cholestasis, Gilbert syndrome diagnostics, UGT1A1 gene polymorphism

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ЖИЛЬБЕР СИНДРОМЫ: КЛИНИКАЛЫҚ ЖАҒДАЙ ЖӘНЕ ҚАЗІРГІ ДИАГНОСТИКА ҚҰРАЛДАРЫНА ШОЛУ

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16-жастағы жігіт тамағының, тізе буындарының ауырсынуы мен жалпы әлсіздік шағымдарымен жоспарлы тонзиллэктомия жасау үшін ауруханаға түсті. Жоспарлы ота жасау алдындағы лабораториялық зерттеулер жалпы және тіке емес билирубиннің жоғарылауын және басқа бауыр тесттерінің жағынан өзгеріс жоғын көрсетті. Тіке емес билирубиннен басқа бауыр анализдеріндегі өзгерістің және вирус, токсин және алкоголь салдарынан гепатит белгілерінің жоқтығы негізінде, анамнездегі бірқатар сарғаю жағдайларын есепке ала отырып Жильбер синдромы диагнозы қойылды. Бұл диагноз кейін UGT1A1 генінің мутациясы анализін тапсыру арқылы дәлелденді. Жильбер синдромы популяцияның 10%-да кездесіп, билирубин айналымының туа біткен ең жиі ауруы болып саналады. Билирубиннің тек тіке емес фракция есебінен жоғарылап, оның жалпы науқас денсаулығына және өмір сүру ұзақтығына әсер етпеуі Жильбер синдромының айқын сипаты болып табылады. Жильбер синдромының диагнозы басқа бауыр ауруларын жоққа шығару негізінде, немесе қиын диагностикалық жағдай туындай қалғанда UGT1A1 генінің мутациясын анықтау арқылы қойылады.

Маңызды сөздер: Жильбер синдромы, гипербилирубинемия, холестаз, Жильбер синдромының диагностикасы, UGT1A1 ген полиморфизмі

СИНДРОМ ЖИЛЬБЕРА: КЛИНИЧЕСКИЙ СЛУЧАЙ И ОБЗОР ДОСТУПНЫХ МЕТОДОВ ДИАГНОСТИКИ

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Юноша 16 лет поступил в клинику с жалобами на боли в горле, боли в коленных суставах и общую слабость для выполнения плановой тонзиллэктомии. Лабораторное обследование на предоперационном этапе показало гипербилирубинемию преимущественно за счет непрямой фракции при отсутствии изменений со стороны других печеночных тестов. На основании стойко нормальных печеночных тестов, за исключением непрямой гипербилирубинемии, у юноши с отсутствием данных за токсическое, метаболическое и вирусное поражение печени и неоднократными эпизодами желтухи в анамнезе, был диагностирован синдром Жильбера, который был позднее подтвержден результатами теста на мутации гена UGT1A1. Синдром Жильбера является самым частым генетически обусловленным заболеванием, ассоциированным с нарушением обмена билирубина, встречаясь в среднем у 10% популяции. Отличительной особенностью синдрома Жильбера является непрямая гипербилирубинемия, достоверно не влияющая на прогноз и продолжительность жизни пациентов. Диагноз синдрома Жильбера может быть выставлен методом исключения, в трудных диагностических случаях возможно применение теста на мутации гена UGT1A1.

Ключевые слова: синдром Жильбера, гипербилирубинемия, диагностика синдрома Жильбера, полиморфизм гена UGT1A1

INTRODUCTION

Gilbert syndrome is the most prevalent inherited disorder of bilirubin metabolism in humans, affecting up to 10% of the population[1]. Nonhemolyticunconjugated hyperbilirubinemia, without any effect on prognosis and life expectancy of the patient is the distinctive feature of Gilbert syndrome. Gilbert syndrome is usually diagnosed by exclusion of other more prevalent liver diseases, in difficult diagnostic situations use of UGT1A1 gene mutation is advised.We hereby report a case of Gilbert syndrome, discovered by chance in a young male, prior to undergoing an operation.

CASE REPORT

A 16-year old Caucasian male was admitted with complaints on sore throat, unilateral knee joint pain and general weakness. His medical history was unremarkable.There were no risk factors of viral hepatitis, except tonsillectomy at the age of 4. The patient did not report taking any medicationson a regular basis, including over the counter ones.

At the initial examinataion the patient appeared to be astenicperson with BMI 18. Physical examination revealed intraoral hyperemy and stage 2 tonsils enlargement and was unremarkable with no chronic liver disease stigmata. The decision was made to proceed with tonsillectomy and the patient was evaluated for pre-operation lab check(table 1).

Table 1. Relevant laboratory findings on pre-operation lab check at day 1

Analysis	Lab values	Normal values range
White cell count (WBC)	6.7	4.8-8.8*10^9/l
Haemoglobin (Hb)	140	120-150 g/l
Platelets (PLT)	223	180-320*10^9/l
Erytrhocyte sedimentation rate (ESR)	5	0-10 mm/h
Total bilirubin	48	0-22.2 µmol/l
Unconjugated bilirubin	40	0-17.1 µmol/l
Alanine transaminase (ALT)	11	7-40 U/l
Aspartate transaminase (AST)	18	7-33 U/l
γ-glutamyltransferase (GGT)	38	15-85 U/l
Alkaline phosphatase (ALP)	49	0-117 U/l
Total protein (TP)	68	60-80 g/l
Creatinine	67	53-115 µmol/l
Glucose	5.1	3.5-5.5 mmol/l
HBsAg	Negative	Negative
HCV Ab	Negative	Negative
HIV Ab	Negative	Negative

Pre-operation lab check revealed normal values of all liver tests except of hyperbilirubinemia due to elevated unconjugated bilirubin. Young age of patient and slim body composition excluded diagnosis of alcoholic liver disease and nonalcoholic fatty liver disease. Thorough anamnesis check involving interview with the parents revealed repetitive episodes of yellowing of the whites of the eyes in the patient starting from the early childhood, lasting for several days and recovering spontaneously. Due to unremarkable abdominal ultrasound with no apparent signs of liver/biliary disease and portal hypertensionand negative results of viral hepatitis serology, preliminary diagnosis of Gilbert syndrome was made.

Due to noabsolute contraindications for the tonsillectomy, the operation was performed on the 2nd day of admission. Subsequent laboratory evaluation on days three and six of admission revealed no change in liver tests other than mild improvement in bilirubin values (table 2).

Table 2. Laboratory findings on the 3rd and 6th day of admission

Analysis	3rd day	6th day	Normal values range
Total bilirubin	**65**	**36**	0-22.2 μmol/l
Unconjugated bilirubin	**55**	**30**	0-17.1μmol/l
Alanine transaminase (ALT)	14	18	7-40 U/l
Aspartate transaminase (AST)	16	17	7-33 U/l
γ-glutamyltransferase (GGT)	41	39	15-85 U/l
Alkaline phosphatase (ALP)	46	51	0-117 U/l

The patient was discharged and normal values of total and unconjugated bilirubin on outpatient follow-up a month later were demonstrated.Upon discharge the test for UGT1A1 gene mutation was performed, which revealed changes, consistent with the diagnosis of Gilbert syndrome.

DISCUSSION

Gilbert syndrome is the most prevalent inherited disorder of bilirubin metabolism.The condition was first described by Gilbert Augustin and Lereboullet Pierremore than 100 years ago[2] and some half a century later glucuronyltransferase deficiency was proved as a cause of the disease [3]. Information on prevalence of this condition in Kazakhstan is lacking, it is known to affect upto 10% of the US population with male to female ratio of 2-7:1[1]. Being a benign genetic condition, it presents with almost exclusive elevation of unconjugated fraction of serum bilirubin, which resolves spontaneously and need no special treatment, apart from supportive care.Patients may occasionally report vague abdominal discomfort and general fatigue, which may lead to number of unnecessary investigations.

Several diagnostic tests have been proposed to identify patients with Gilbert syndrome, including caloric restriction, phenobarbital test[4], nicotinic acid and rifampicin test[5], drug clearance and thin-layer chromatography test. Fasting is the simplest of all tests, demonstrating 2- to 3-fold increase of serum unconjugated bilirubin within 48 hours of caloric restriction (usually up to 400 kcal/day) and return to normal values in 24 hours of normal diet resumption. Similar rise in serum unconjugated bilirubin, but much faster (usually within 3 hours), may be achieved by intravenous administration of 50 mg of nicotinic acid. Due to such a rise in plasma unconjugated bilirubin may be also seen in patients with hemolysis or liver disease, these tests cannot be considered truly diagnostically accurate. Phenobarbital administration leads to normalization of bilirubin levels in paients with Gilbert syndrome due to accelerated bilirubin clearance and it's reduced turnover, same can be achieved by steroids. Thin-layer chromatography was one of the most accurate tests for Gilbert syndrome in pre-genetic testing era, showing reduced uridinediphosp hateglucuronyltransferase activity. Since the discovery of genetic polymorphisms in the UGT1A1 gene, responsible for Gilbert syndrome, diagnostic confusion chances are almost eliminated. Most of the cases are related with seven instead of six repeats in bilirubin uridinediphosphateglucuronyltransf erase gene (UGT1A1*28) (Bosma 1995). T to G substitution in the UGT1A1 gene (UGT1A1*60) may co-occur with the UGT1A1*28 polymorhism, being the second most prevalent finding in genetic testing for Gilbert syndrome]6].

The presented case may well be an usual example in the clinical practice of virtually any medical specialist. The one should be aware of the existence of this inherited genetic condition and of the available diagnostic approaches, which may prevent unnecessary investigations and help to diagnose Gilbert syndrome even in difficult clinical situations.

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