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Statin-induced acute liver injury: case report, review of available literature and algorithm of management

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59-year old female was admitted with general weakness, yellowing of the whites of the eyes and right upper quadrant abdominal discomfort. She was started on atorvastatin therapy 5 days prior to admission. Laboratory investigations showed significant elevations of markers of liver cell injury and cholestasis. As soon as the statin has been withdrawn, lab evaluation showed marked improvement in liver tests, proving the diagnosis of stain-induced liver injury. Statins' use may be associated with liver enzymes abnormalities, ranging from asymptomatic transaminase elevation to hepatitis, cholestatis and acute liver failure. Published evidence suggests that statins generally are well tolerated, cases of severe liver injury are extremely rare. Thus, liver tests evaluation prior to statin therapy start is warranted for all patients and close monitoring for those with liver disease and/or abnormal liver enzymes.

Key words: statin hepatotoxicity - atorvastatin - drug-induced liver injury - atorvastatin-induced liver injury - statin-induced liver injury management

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СТАТИНДІ ПАЙДАЛАНУ САЛДАРЫНАН ПАЙДА БОЛҒАН БАУЫРДЫҢ ЖІТІ ҚАБЫНУЫ: КЛИНИКАЛЫҚ ЖАҒДАЙ, ӘДЕБИЕТКЕ ШОЛУ ЖӘНЕ НАУҚАСТЫ ЖҮРГІЗУ АЛГОРИТМІ

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59-жастағы әйел жалпы әлсіздік, көз ақтарының сарғаюы және іштің жоғарғы оң жағының ауырсынуымен ауруханаға түсті. Ауруханаға түсуден бұрын 5 күн бұрын аторвастатин ішуді бастаған. Лабораториялық зерттеулер нәтижесінде бауыр жасушаларының зақымдалуы мен холестаз белгілері бары анықталды. Статин тоқтатыла сала жүргізілген қайта лабораториялық зерттеу бауыр зақымдалу белгілерінің жақсаруын көрсетіп, статин пайдалану салдарынан туған бауыр зақымдалу диагнозын растады. Статиндерді пайдалану бауыр ферменттерінің өзгеруін, симптомсыз трансаминиттен гепатит, холестаз және жіті бауыр жетіспеушілігіне дейін, тудыруы мүмкін. Зерттеулер нәтижесіне сүйенсек науқастар статиндерді жалпы жақсы көтереді, бауырдың жіті жетіспеушілігіне әкеліп соқтыру жағдайлары өте сирек кездеседі. Дегенмен, статинді бастамас бұрын барлық науқастар лабораториялық зерттеуден өтуі қажет, бауыр ферменттерінің өзгеруі және/немесе бауыр ауруы болған жағдайда мұқият тексеріліп тұрғандары жөн.

Маңызды сөздер: статин пайдалану салдарынан бауырдың зақымдалуы, аторвастатин, аторвастатин пайдалану салдарынан бауырдың зақымдалуы, дәрі пайдалану салдарынан туған гепатит.

ОСТРОЕ ПОРАЖЕНИЕ ПЕЧЕНИ, АССОЦИИРОВАННОЕ С ИСПОЛЬЗОВАНИЕМ СТАТИНА: КЛИНИЧЕСКИЙ СЛУЧАЙ, ОБЗОР ЛИТЕРАТУРЫ И АЛГОРИТМ ВЕДЕНИЯ.

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Женщина 59 лет поступила в клинику с жалобами на общую слабость, иктеричность склер и дискомфорт в правой подреберной области. За 5 дней до поступления в клинику она начала прием аторвастатина. Лабораторное обследование показало значительный рост маркеров цитолиза и холестаза. Повторное лабораторное обследование после отмены статина продемонстрировало значимое снижение трансаминаземии, свидетельствуя в пользу статин-индуцированного острого поражения печени. Применение статинов может ассоциироваться с повышением активности ферментов печени различной степени выраженности, от бессимптомного трансаминита до гепатита, холестаза и острой печеночной недостаточности. Данные исследований демонстрируют, что в целом, статины хорошо переносятся, а случаи выраженного повреждения печени чрезвычайно редки. Всем пациентам до начала терапии статинами показано лабораторное обследование ферментов печени, в случаях повышения активности их и/или заболевания печени – тщательный мониторинг.

Ключевые слова: статин-индуцированное поражение печени - аторвастатин - аторвастатин-индуцированное поражение печени - токсический гепатит - лекарственный гепатит

INTRODUCTION:

Statins are among most widely used drugs worldwide due to their beneficial effect on primary and secondary prevention of coronary heart disease [1]. Since introduction in late ‘80s, safety concerns have been raised related to the development of liver and muscle injury, while on statin therapy [2]. We hereby report a case of adverse effect of statin use, successfully resolved by the drug withdrawal, review of available literature and algorithm of management of patients.

CASE REPORT

A 59-year old Asian female was admitted with increased frequency and intensity of headache in occipital zone, general weakness, yellowing in whites of the eyes and right upper quadrant abdominal discomfort. She had medical history of blood hypertension and ischemic heart disease for more than 10 years and successful hysterectomy due to hysteromyoma. There were no risk factors of viral hepatitis. Her regular maintenance therapy included enalapril 20 mg/daily, nebivolol 5 mg/daily, trimetazidine 35 mg/daily and aspirin 75 mg/daily. 5 days prior to admission she was started on atorvastatin 20 mg/daily by her outpatient cardiologist in addition to her regular medications listed above. The patient did not report taking any medications other than listed, including over the counter ones.

She appeared to be well developed and nourished person with BMI 27 and mild yellowing in the whites of the eyes. Physical examination revealed high blood pressure 180/100 mm Hg with regular heart rate of 78/min, but was otherwise unremarkable with no chronic liver disease stigmata. She was promptly managed with antihypertensives for her high blood pressure and was evaluated for the cause of jaundice (table 1).

Considering unremarkable abdominal untrasound with no apparent signs of liver/biliary disease and portal hypertension and negative results of viral hepatitis A, B and C serology, preliminary diagnosis of acute liver injury secondary to atorvastatin use was made. Atorvastatin was withdrawed and the patient was managed with intravenous fluids. The diagnosis was confirmed by subsequent laboratory evaluation on days four and seven of admission (3rd and 6th day of atorvastatin withdwaral), which revealed significant improvement in liver biochemistry (table 1).

Table 1. Relevant laboratory findings on admission and on the 4th and 7th day of admission (3rd and 6th day of atorvastatin withdrawal)

Analysis	Admission	4th day	7th day	Normal values range
White cell count (WBC)	5.3			4.8-8.8*10^9/l
Haemoglobin (Hb)	128			120-150 g/l
Platelets (PLT)	255			180-320*10^9/l
Total bilirubin	**40**	**15**		0-22.2 μmol/l
Conjugated bilirubin	27	4		0-5.1 μmol/l
Alanine transaminase (ALT)	**519**	**296**	**99**	7-40 U/l
Aspartate transaminase (AST)	**520**	**103**	**31**	7-33 U/l
γ-glutamyl transferase (GGT)	911	412		15-85 U/l
Alkaline phosphatase (ALP)	178	127		0-117 U/l
Creatine kinase (CK)	20			24-145 U/l
Creatinine	36			53-115 μmol/l

The patient was discharged and normal values of aminotransferases on outpatient follow-up two weeks later were demonstrated.

DISCUSSION

Statins are among most widely used drugs worldwide due to their beneficial effect on primary and secondary prevention of coronary heart disease. They undergo first-pass liver hepatic metabolism, inhibiting HMG-CoA reductase, this way blocking synthesis of endogenous cholesterol in the liver. Since introduction in late '80s, safety concerns have been raised related to the development of liver and muscle injury, while on statin therapy. Different scenarios of liver involvement secondary to statin use were reported, ranging from asymptomatic elevation of ALT and AST, also known as "transaminitis", to cholestasis, hepatitis and acute liver failure (ALF) [3]. Although declared as possible, development of ALF while on statin therapy is extremely rare with rate of about 0.2 cases per million in United States, which is less than risk of idiopathic ALF in the general population – 0.5-1.0 case per million [2]. In real life setting, much more common are elevations of ALT >3 times the upper level of normal (ULN) during first 12 weeks of treatment, which occurred in 1.3% of patients on statin therapy (10-40 mg/daily of simvastatin or lovastatin or fluvastatin or atorvastatin or pravastatin) compared to 1.1% of patients taking placebo, according to combined survey of three meta-analyses of controlled trials [4]. Available data suggest, that asymptomatic ALT elevations secondary to statin use return to normal values in most cases, even if the same drug is continued [5]. No clinical sequelae following ALT elevations has resulted in some authors not considering those a true drug hepatoxicity, which should also include elevated total bilirubin (>2 times ULN) levels, according to Hy Rule criteria [6]. In fact, no published evidence of statin-induced liver damage chronic carriers is available up to date [7].

In the current era of obesity and metabolic syndrome, physicians often face a challenge of administering a statin to a patient with elevated transaminase levels (figure 1).

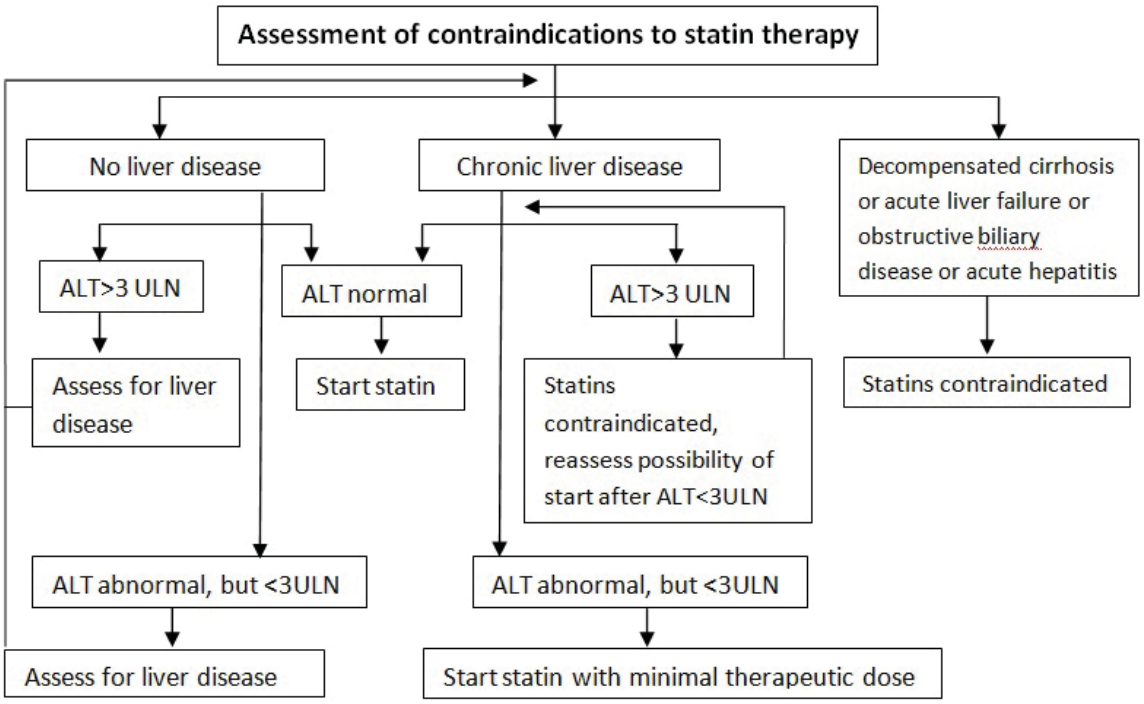

Figure 1. Algorithm of assessment of contraindications to statin therapy. ALT – alaninaminotransferase, ULN – upper limit of normal

According to a survey from 1999 to 2002, ALT elevation was present in 8.9% of US population [7]. Most of these cases are related to nonalcoholic fatty liver disease, viral hepatitis B and C and alcoholic liver disease, which raises the issue of balance of statin therapy's benefit and risk of liver injury. Recent data suggest, that statins may in fact be safely administered and used long-term in patients with NAFLD and preexisting ALT elevations, provided the appropriate monitoring is exercised [8]. Statins have also been demonstrated to be used in patients with chronic hepatitis C and according to controlled trials even possess, fluvastatin particularly, antiviral activity against HCV both in vitro and in vivo [9]. US Food and Drug Administration (FDA) consistently reviewed post-marketing data on statin-induced serious liver injury and concluded that the risk was extremely low (reporting rate to Adverse Event Reporting System of ≤2 per one million patient-years) and unpredictable in individual patients, thus abolishing the need to constantly monitor liver tests while on statin therapy unless clinically indicated [10]. Still, decompensated cirrhosis, acute liver failure and obstructive biliary disease remain contraindications for statin use. Patients with acute liver disease (acute hepatitis B and C, alcoholic hepatitis) should be spared from statin use until liver tests return to normal values.

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