

Case Report

Anti-Dementia Drugs and Hepatotoxicity—Report of Two Cases

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ARTICLE INFO

Article history:

Received 13 July 2017

Received in revised form

25 November 2017

Accepted 17 January 2018

Available online 2 March 2018

Keywords:

drug-induced liver injury,

alzheimer's disease,

anti-dementia drugs,

elderly

SUMMARY

Two patients with Alzheimer's disease who developed hepatitis caused by anti-dementia drugs are presented. Case 1: An 84-year-old-woman was referred to our hospital with profound jaundice. The levels of liver enzymes and jaundice decreased after the cessation of memantine and yokukansan (herbal medicine approved for dementia in Japan). Case 2: An 82-year-old-man was referred because of elevated transaminases. Liver biopsy showed central necrosis typical for drug-induced liver injury. The levels of transaminases decreased after withdrawal of rivastigmine transdermal patch treatment. Anti-dementia drugs have been safely used in terms of hepatotoxicity. However, some cases might be missed because of the difficulty in recognizing signs and symptoms in elderly and dementia patients.

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1. Introduction

Dementia is one of the biggest health concerns in an aging society. There are almost 5 million patients with dementia in Japan, and a steep increase in the prevalence of Alzheimer's disease in elderly people has been reported.¹

Currently there are two types of drug therapies for dementia, choline esterase inhibitors and N-methyl-D-aspartate (NMDA) channel blockers. Of them, Donepezil hydrochloride was approved in US (1996) and Japan (1999), followed sequentially by rivastigmine, galantamine, and memantine in Japan since 2011.

In Japanese nationwide survey for drug-induced liver injury (DILI), 10.1% of the cases were caused by psychiatric and neurological drugs.² However, there have been no reports on the incidence of DILI induced by anti-dementia drugs in a large population. In fact, only a few case reports of hepatic toxicity caused by anti-dementia drugs have been reported so far.^{3–5} This may partly be due to the difficulties in recognizing symptoms in elderly persons with mental disabilities. The cases of two patients who had liver injury caused by anti-dementia drugs are presented.

2. Patients (Laboratory data in Table 1)

2.1. Patient 1

An 84-year-old woman was referred to our hospital on July 27, 2016 with jaundice. She had been treated with memantine (10 mg/day) and yokukansan (7.5 gr/day) for Alzheimer's disease since March 2016. She was also taking chlorpromazine hydrochloride and aspirin for a long time. Her general condition was good except for profound jaundice. The patient had no history of liver diseases, alcohol intake, intravenous drug use, intake of supplements, or blood transfusion. Laboratory tests showed an aspartate aminotransferase (AST) level of 99 IU/L (reference range 5–40 IU/L), alanine aminotransferase (ALT) 119 IU/L (5–40 IU/L), alkaline phosphatase (ALP) 1506 IU/L (110–350 IU/L) and total bilirubin (TB) 16.6 (direct 11.9) mg/dl (0.2–1.2 mg/dl). Prothrombin time was 119.5% (INR 0.92). She was negative for HBsAg, anti-HCV, IgM-anti-HAV, and anti-nuclear antibodies. The eosinophil count was mildly elevated (6.3%). Contrast-enhanced CT showed no biliary stones or tumors. After memantine (10 mg/day) and yokukansan were stopped, the liver enzyme levels decreased gradually and became 28/29 IU/L for AST/ALT, 764 IU/L for ALP and 3.4 mg/dl for TB on August 31. Lymphocyte transformation tests (LTTs) were positive for yokukansan and negative for memantine. The AST/ALT returned to 23/24 IU/L at the last visit to the hospital the following February.

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Table 1
Laboratory data of the patients.

<u>Patient 1</u>				<u>Patient 2</u>			
WBC, / μ L	6600	PT, %	119.5	WBC	5700	PT	82.4
Seg, %	67.3			Seg	66.2		
Eosino, %	6.3	HBsAg	(-)	Eosino	1.1	HBsAg	(-)
Baso, %	1.2	Anti-HCV	(-)	Baso	0.4	Anti-HCV	(-)
Mono, %	6.6	IgM-HA	(-)	Mono	9.3	ANA	X40
Lympho, %	18.6	ANA	<X40	Lympho	23.0	IgG	1360
		IgG, (mg/dl)	1930			IgA	242
Hb, g/dL	11.1	IgA, (mg/dl)	338	Hb	12.1	IgM	163
		IgM, (mg/dl)	205			AM2A	(-)
TP, (g/dL)	6.6			TP	6.9		
Alb, (g/dL)	2.7			Alb	3.9		
T-bil, (mg/dL)	16.6	LTT, Stimulation index (%)		T-bil	1.2		
D-bil, (mg/dL)	11.9	memantine 107 (-)		D-bil	0.2		
AST, (IU/L)	99	yokukansan 529 (+)		AST	417		
ALT, (IU/L)	119			ALT	532		
LDH, (IU/L)	211			LDH	399		
ALP, (IU/L)	1506			ALP	378		
γ -GTP, (IU/L)	449			γ -GTP	101		
Ch-E, (IU/L)	148			ChE	63		

2.2. Patient 2

An 82-year-old man was referred to our hospital on April 11, 2017 with elevated liver enzyme levels. Laboratory tests showed levels of 417/532 IU/L for AST/ALT, 378 IU/L for ALP, and 1.2 mg/dl for TB. He was negative for HBsAg, anti-HCV, and anti-nuclear and anti-mitochondrial antibodies. Serum immunoglobulin levels were normal. There were no abnormalities on physical examination. He had no history of liver diseases, alcohol intake, intravenous drug use, intake of supplement, or blood transfusion. He was once hospitalized with benign rectal ulcers in December 2016, when a transdermal patch of rivastigmine (4.5 mg/day) was started for Alzheimer's disease. Since then, his chronic medications (anti-acid drug and laxative) have been unchanged, except that midodrine hydrochloride was started in March 2017 for orthostatic hypotension. The dose of rivastigmine was increased to 9 mg in January 2017. Although midodrine hydrochloride was stopped after referral to our hospital for its possible association with hepatitis, liver enzymes continued to increase to AST/ALT = 417/532 IU/L, ALP = 378 IU/L on May 2. Liver biopsy was performed on May 10, and rivastigmine was stopped as the suspected causative drug on May 11. The liver enzymes levels decreased and became 32/28 IU/L for AST/ALT on June 22. At that point, 4.5 mg of rivastigmine was started and stopped on July 20, because of the re-elevation of AST/ALT (50/37 IU/L).

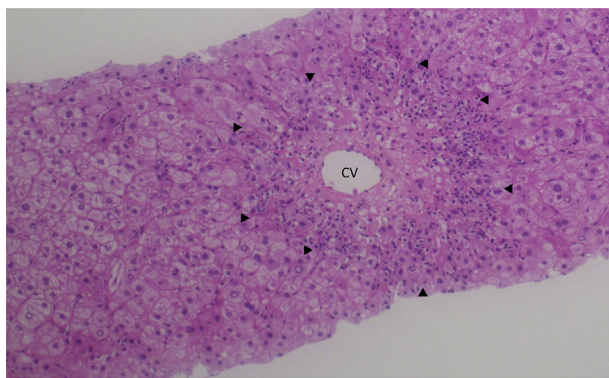
Informed consent and approval for publication were obtained from the patients. Careful attention was paid to protect the patients' personal information.

3. Discussion

Reports of DILI with anti-dementia drugs have been rare. A recent two-year nationwide survey in Iceland and a three-year population-based study in France on DILI showed no cases of anti-dementia DILI among 96 and 34 patients, respectively.^{6,7} In the previous literature, a case of cholestatic hepatitis induced by memantine was reported in 2008,³ and hepatic injury by rivastigmine was reported in 2009.⁴ These authors argued that these

were the first DILI cases caused by each drug. Reports on donepezil hydrochloride, which has been used for a longer time, are also rare, including one with a fulminant hepatitis caused by its combination with a serotonin reuptake inhibitor in 2000.⁵ Consequently, anti-dementia drugs have been generally accepted as safe. However, it is difficult to recognize signs and symptoms of hepatic injury in mentally disabled elderly persons. Thus, subclinical hepatotoxicities with these drugs might be more prevalent. Since elderly people have complications and are on many other drugs, it is also necessary to consider that blood concentrations tend to be high due to drug interactions.⁸

The cases of two elderly patients with hepatic injury induced by anti-dementia drugs were described. In the first patient, liver injury may have been caused by either memantine or yokukansan, because liver function tests improved after the withdrawal of the drugs. Total score calculated according to the Japan's diagnostic criteria for DILI in 2004 was more than 5 points for both drugs, where the most probable score was 5 or more.⁹ Yokukansan is a Japanese herbal medicine approved for use for behavioral and psychological symptoms of dementia (BPSD).¹⁰ Japan's diagnostic guidelines for DILI include the result of a lymphocyte transformation test (LTT) for the identification of causative agent.⁹ Only yokukansan was positive. However, this result should be considered with caution because herbal medicines tend to cause false positive results with this test.¹¹ In addition, there have been no case reports of DILI with yokukansan in Pubmed. Thus it may be impossible to identify which drug was the cause. In the second patients, a rivastigmine transdermal patch was considered to be a causative agent because transaminitis improved after cessation of the drug. Liver histology showed a figure of DILI with central zone hepatic necrosis¹² (Fig. 1). This centilobular (zone 3, area around the terminal hepatic venule) necrosis is a typical hepatocellular injury pattern of DILI.¹³ The total diagnostic score was 8 points, that was the most probable. In addition, duration to onset of DILI was about 3 and 4 months for patient 1 and 2, respectively, which is reasonable to consider them as causative agents chronologically.



CV: Central Vein

Fig. 1. Liver biopsy specimen obtained from patient 2 shows a necrotic area around the central vein with infiltration of lymphocytes.

The difficulty to recognize symptoms and signs of hepatitis in elderly and mentally ill patients might result in some patients who develop hepatitis, especially at the subclinical stage, being missed. Clinicians should check liver functions regularly in such patients to detect liver injury early before it becomes severe.

Ethical approval

Informed consent and approval for publication were obtained from the patients. Ethical approval from the committee is not required because case reports do not belong to the category of Japan's ethical guidelines on human medical research (March 31, 2017).

Conflicts of interest

We declare that there are no potential financial and non-financial conflicts of interests.

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