

# Parkinsonian syndrome and ataxia as a presenting finding of acquired hepatocerebral degeneration

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Miletić, Vladimir; Ozretić, David; Relja, Maja

Source / Izvornik: **Metabolic Brain Disease, 2014, 29, 207 - 209**

Journal article, Accepted version

Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

<https://doi.org/10.1007/s11011-013-9478-z>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:699774>

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## Središnja medicinska knjižnica

**Miletić V., Ozretić D., Relja M. (2014) *Parkinsonian syndrome and ataxia as a presenting finding of acquired hepatocerebral degeneration*. *Metabolic Brain Disease*, 29 (1). pp. 207-9. ISSN 0885-7490**

<http://www.springer.com/journal/11011>

<http://link.springer.com/journal/11011>

<http://dx.doi.org/10.1007/s11011-013-9478-z>

<http://medlib.mef.hr/2363>

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**Complete title:** Parkinsonian Syndrome and Ataxia as a Presenting Finding of Acquired  
Hepatocerebral Degeneration

**Authors:** Vladimir Miletic<sup>1</sup>, David Ozretić<sup>2</sup>, Maja Relja<sup>1</sup>

**Affiliations:** <sup>1</sup>University of Zagreb, School of Medicine and University  
Hospital Centre Zagreb, Department of Neurology,  
Kišpatićeva 12, 10000 Zagreb, Croatia  
<sup>2</sup>University of Zagreb, School of Medicine and University  
Hospital Centre Zagreb, Department of Radiology,  
Kišpatićeva 12, 10000 Zagreb, Croatia

**Corresponding author:** Vladimir Miletic  
<mailto:vladimir.miletic@gmail.com>  
Phone number: 00385 1 2388 345  
Fax number: 00385 1 2388 377

## **Abstract**

The term “acquired hepatocerebral degeneration” (AHD) was coined to describe clinical entity distinct from genetically defined Wilson’s disease. AHD is chronic neurological disorder, characterized by extrapyramidal and neuropsychiatric symptoms accompanied with advanced liver disease with portosystemic shunts. In majority of AHD cases, extrapyramidal symptoms appear in the presence of known liver disease. Here we present a patient with subacute onset of bilateral, asymmetric, hypokinetic-rigid syndrome and ataxia as initial presentation of liver cirrhosis. Manganese toxicity have major role in AHD pathogenesis. Failure of liver detoxification and presence of portosystemic shunting enables neurotoxic substance of manganese to avoid hepatic metabolism and to enter and accumulate in central nervous system. Predilection brain regions for manganese deposits are globus pallidum (GP) and substantia nigra (SN). Characteristic MRI findings of bilateral, symmetrical hyperintensities of GP and SN on T1-weighted sequences supported the diagnosis of AHD in our patient. In addition, increased T2 signal in dentate nuclei seen in our patient is rare radiological finding. So far, no consensus guidelines regarding medical treatment of AHD exist. We initiated low-dose levodopa treatment, but failed to provide beneficial effect. In conclusion, AHD is distinct clinical entity that should be included in differential diagnosis of both typical and atypical parkinsonian syndromes. Furthermore, our case highlights the importance of performing MRI in patients with atypical parkinsonism.

Keywords: Acquired hepatocerebral degeneration; Parkinsonism in cirrhosis; Magnetic resonance imaging; Manganese

# **Parkinsonian Syndrome and Ataxia as a Presenting Finding of Acquired Hepatocerebral Degeneration**

Introduction:

Connection between liver diseases and central nervous system (CNS) impairment has been well established. One century after description of neurological dysfunction associated with cirrhosis unrelated to Wilson's disease (van Woerkom 1914), relationship between brain disorders and abnormal liver function still intrigues the scientific community. In 1965, the term "acquired hepatocerebral degeneration" (AHD) was coined to describe clinical entity distinct from genetically defined Wilson's disease (Victor et al. 1965). AHD is chronic neurological disorder characterized by extrapyramidal and neuropsychiatric symptoms accompanied with advanced liver disease with portosystemic shunts (Ferrara and Jankovic 2009; Butterworth 2012). Multifarious clinical manifestation of AHD includes cognitive decline, apathy, somnolence, ataxia, myelopathy, dysarthria, and wide variety of abnormal movements such as parkinsonism, dystonia, cranial dyskinesias and chorea. Having diverse clinical manifestation AHD may mimic a broad range of disease. Here we present a patient with parkinsonian syndrome and ataxia as initial presentation of liver cirrhosis.

Case presentation:

A 57-year-old female was hospitalized at movement disorders unit for evaluation of subacute onset, hypokinetic-rigid syndrome. Patient described having stiffness and pain in her shoulders and sense of generalized slowness. She also noticed her left arm being "clumsy". Her symptoms started gradually during ten months prior to hospital admission. Patient's husband revealed that his wife experienced several episodes of disorientation and impaired concentration with spontaneous resolution within 24 hours. Her past medical history included cholecystectomy, hysterectomy and adnexectomy due to myoma and ovarian cysts. There was

no prior history of parkinsonism, carbon monoxide poisoning, CNS infection, neuroleptic and toxin exposure. She denied the presence of any neurological diseases in her family, but confessed daily consumption of 200 – 500 ml of red wine. She was not taking any medical therapy on admission. On initial examination she was alert and orientated, scoring 27/30 on Mini Mental State Examination mostly due to impaired attention. Her voice was mildly hypophonic and she had reduced facial expression. Bilateral asymmetric rigidity and bradykinesia, more severe on her left extremities were present. Low-amplitude postural tremor was observed. She walked on wide base with short steps and had reduced left arm swing. Balance impairment on retropulsion test was present. Deep tendon reflexes were symmetric and none of the pathologic reflexes were induced. Laboratory examination revealed thrombocytopenia (77,000 platelets/dl), abnormal coagulation profile with prothrombin activity 62%, abnormal liver function tests (AST 45 IU/L; GGT 88 IU/L; total bilirubin 49 mg/dl; direct bilirubin 14 mg/dl), total protein 59 g/L, albumin 31 g/L and high ammonia level of 143  $\mu$ mol/L. Red and white blood cell count, erythrocyte sedimentation rate, electrolyte panel, urea, creatinine, alkaline phosphatase, albumin/globulin ratio, IgG, IgA, IgM, thyroid function tests, vitamin B12 and folic acid levels were all within the normal range. Abdominal ultrasound revealed features consistent with cirrhosis including dilatation of coronary vein. Normal concentration of ceruloplasmin, serum and urine copper and absence of Kayser-Fleischer ring excluded Wilson's disease. Tumour markers (AFP, CEA, CA 125, CA 19-9), antinuclear antibody, antimitochondrial antibody and liver-kidney microsomal antibody levels were normal. Serological testing for hepatitis A, hepatitis B and hepatitis C was negative. Magnetic resonance imaging (MRI) of the brain was performed and showed diffuse brain atrophy, symmetrically increased signal in substantia nigra (SN) and globus pallidum (GP) on T1-weighted sequences (Fig. 1), and increased T2 signal within both dentate nucleus (Fig. 2). According to clinical and radiological data, we made the diagnosis of

alcoholic liver cirrhosis grade B9 of the Child Pugh classification, with parkinsonian syndrome and mild encephalopathy as neurological complications in spectrum of AHD condition. Short-term, low-dose levodopa treatment was tried, but failed to provide beneficial effect. We have referred our patient to gastroenterologist for further diagnostic procedures and treatment.

#### Discussion:

Liver diseases may cause a variety of neurological impairment, with hepatic encephalopathy being most common. The prevalence of AHD among patients with cirrhosis varies between 1-21% (Butterworth 2012; Burkhard et al. 2003). In contrast to acute onset and treatment responsive hepatic encephalopathy, AHD represents chronic disorder, highly resistant to treatment. AHD – related parkinsonism is characterized by rapid progression, bilateral and mostly symmetrical bradykinesia, rigidity, action and postural tremor, postural instability and shuffling gait. However, mild side predominance like in our patient can be seen (Burkhard et al. 2003). In majority of AHD cases published so far, extrapyramidal symptoms usually appear in presence of known liver disease. There are only few reports similar to ours that presented patient with parkinsonian syndrome and ataxia as initial manifestation of the occult cirrhosis (Noone et al. 2008).

Manganese toxicity have major role in AHD genesis, although impact of ammonia and aromatic amino acid should not be disregarded. More recently, mutation in *SLC30A10* (Solute Carrier Family 30, Member 10) gene, encoding a manganese transporter was discovered as a cause of inherited, inborn error of manganese metabolism (Tuschl et al. 2012). This autosomal recessive condition has similar phenotypical manifestation as AHD, but onset of symptoms is usually in childhood compared to AHD. Several investigations demonstrated increased manganese levels in blood, cerebrospinal fluid and brain tissue in patient with liver cirrhosis (Burkhard et al. 2003; Pomier-Layrargues et al. 1995). Failure of liver detoxification

and presence of portosystemic shunting enables neurotoxic substance of manganese to avoid hepatic metabolism and to enter and accumulate in CNS. Predilection brain regions for manganese deposits are GP and SN. Characteristic MRI findings include bilateral, symmetrical hyperintensities of GP on T1-weighted sequences with normal finding on T2-weighted sequences (Fernández-Rodríguez et al. 2010). Increased T2 signal in dentate nuclei seen in our patient is rare radiological finding and has rarely been reported (Park and Heo 2004). Although exact mechanism of manganese induced movement abnormalities is still unknown, nuclear medicine tomography imaging technique studies point to nigrostriatal dopamine system dysfunction as a possible cause (Guilarte et al. 2006). There is paucity of published data regarding medical treatment of AHD and no consensus guidelines exist. Levodopa replacement therapy can provide amelioration of symptoms in some cases (Butterworth 2012). There was a report of significant improvement of parkinsonism with decrease of high signal intensities in GP on follow-up MRI, in patient treated with chelate agent trientine (Park et al. 2008). Marked alleviation and complete reversal of symptoms was observed following liver transplantation (Stracciari et al. 2001), although post-surgical residual extrapyramidal symptoms have been reported as well (Shulman et al. 2003). Less invasive, endovascular occlusion of portal-systemic shunts, was shown to provide beneficial effect in patient with AHD, but relief was temporary (Condat et al. 1999).

In conclusion, AHD is distinct clinical entity that should be included in differential diagnosis of both typical and atypical parkinsonian syndromes. Having in mind diversity in clinical presentation AHD is frequently overlooked condition and putting correct diagnosis remains clinical challenge.



**Acknowledgment:** Supported from Croatian Ministry of Science, Education and Sports

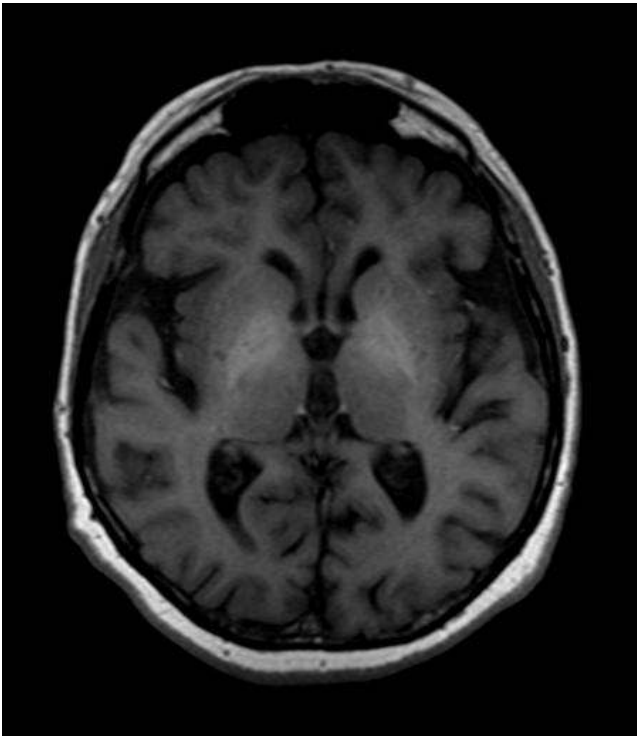
**Conflict of interest:** The authors declare that they have no conflict of interest

References:

1. Burkhard PR, Delavelle J, Du Pasquier R, Spahr L (2003) Chronic parkinsonism associated with cirrhosis: a distinct subset of acquired hepatocerebral degeneration. *Arch Neurol* 60:521-528
2. Butterworth RF (2012) Parkinsonism in cirrhosis: pathogenesis and current therapeutic options. *Metab Brain Dis* 28:261-7
3. Condat B, Dusoleil A, Bernardeau M, Roche A, Pelletier G, Buffet C (1999) Chronic acquired hepatocerebral degeneration: the role of manganese and treatment by endovascular occlusion of a porto-systemic shunt. *Gastroenterol Clin Biol* 23:268-70.
4. Fernández-Rodriguez R, Contreras A, De Villoria JG, Grandas F (2010) Acquired hepatocerebral degeneration: clinical characteristics and MRI findings. *Eur J Neurol* 17:1463-70
5. Ferrara J, Jankovic J (2009) Acquired hepatocerebral degeneration. *J Neurol* 256:320-332
6. Guilarte TR, Chen MK, McGlothan JL, Verina T, Wong DF, Zhou Y, Alexander M, Rohde CA, Syversen T, Decamp E, Koser AJ, Fritz S, Gonczi H, Anderson DW, Schneider JS (2006) Nigrostriatal dopamine system dysfunction and subtle motor deficits in manganese-exposed non-human primates. *Exp Neurol* 202:381-90
7. Noone ML, Kumar VG, Ummer K, Achambat L, Salam KA (2008) Cirrhosis presenting as Parkinsonism. *Ann Indian Acad Neurol* 11:179-81
8. Park HK, Kim SM, Choi CG, Lee MC, Chung SJ (2008) Effect of trientine on manganese intoxication in a patient with acquired hepatocerebral degeneration. *Mov Disord* 23:768-70.
9. Park SA, Heo K (2004) Prominent cerebellar symptoms with unusual magnetic resonance imaging findings in acquired hepatocerebral degeneration. *Arch Neurol* 61:1458-60

10. Pomier-Layrargues G, Spahr L, Butterworth RF (1995) Increased manganese concentrations in pallidum of cirrhotic patients. *Lancet* 345:735
11. Shulman LM, Minagar A, Weiner WJ (2003) Reversal of parkinsonism following liver transplantation. *Neurology* 60:519
12. Stracciari A, Guarino M, Pazzaglia P, Marchesini G, Pisi P (2001) Acquired hepatocerebral degeneration: Full recovery after liver transplantation. *J Neurol Neurosurg Psychiatry* 70:136-137
13. Tuschl K, Clayton PT, Gospe SM Jr, Gulab S, Ibrahim S, Singhi P, Aulakh R, Ribeiro RT, Barsottini OG, Zaki MS, Del Rosario ML, Dyack S, Price V, Rideout A, Gordon K, Wevers RA, Chong WK, Mills PB (2012) Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man. *Am J Hum Genet* 90:457-66
14. van Woerkom W (1914) La cirrhose hépatique avec altérations dans les centres nerveux évoluant chez des sujets d'âge moyen. *Nouvelle Iconographie de la salpêtrière. Clinique des Maladies du Système Nerveux* 7:41-51
15. Victor M, Adams R, Cole M (1965) The acquired (non-Wilsonian) type of chronic hepatocerebral degeneration. *Medicine (Baltimore)* 44:345-396

**Fig. 1** Symmetrically increased signal in globus pallidum on T1-weighted sequences



**Fig. 2** Symmetrically increased signal in dentate nuclei on T2-weighted sequences

