Case Report

Diverse Neurological Symptoms in Chronic Liver Failure: Difficulties in Etiological Diagnosis
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Summary
Acquired hepatocerebral degeneration (AHCD) describes a neurological disorder in the context of chronic hepatic failure which is not related to acute encephalopathy and not explained by an alternative cause. Patients with AHCD may have cognitive deficits, cerebellar findings, hypo- or hyperkinetic movement disorders, and sometimes myelopathy with typical magnetic resonance imaging (MRI) abnormalities, particularly T1 hyperintensity in the internal pallidum.

Here, we report five patients ranging between 45-73 years-old. All had liver disease, four of them were diagnosed as chronic liver failure and one had portosystemic shunts secondary to portal vein thrombosis. Presenting neurological symptoms were parkinsonism (4), ataxia (3), postural and action tremor (3) and cognitive deficit (2). MRI findings were compatible with AHCD.

This report shows the variability of neurological symptoms in AHCD. Possibility of liver disease or portosystemic shunts should be kept in mind before diagnosing any neurodegenerative disease and giving treatments toxic to the liver since neurological symptoms may occur in the presence of normal liver enzymes in some liver diseases causing neurological symptoms.

Key words: Acquired hepatocerebral degeneration, liver failure, tremor, dementia, ataxia

Özet
Edinsel hepatoserebral dejenerasyon (EHSD), akut ensefalopati ile ilişkili olmayan ve başka bir neden ile açıklanamayan, kronik karaciğer hastalığı bağlamında gelişen nörolojik bulguları ifade etmektedir. EHSD hastalarında bilişsel yükme, serebellar bulgular, hipo ya da hiperkinetik hareket bozuklukları ve bazen miyelopati ile tipik manyetik rezonans görüntüleme (MRG) anormallikleri, özellikle internal pallidumda T1 hiperintensite olabilir.

INTRODUCTION

Chronic liver failure is known to cause neurological disturbances, most commonly hepatic encephalopathy. It may include a wide spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction(6) and has usually an acute onset with a fluctuating course. This clinical status should be distinguished from Wilson's disease which itself leads to liver cirrhosis and neurological findings. Acquired hepatocerebral degeneration (AHCD) describes a neurological disorder in the context of chronic hepatic failure which is not related to acute encephalopathy and not explained by an alternative cause(4). Its prevalence has been estimated 0.8-2.0% in chronic liver failure(4,16). Patients with AHCD may have cognitive deficits affecting mainly attention and executive domains, cerebellar findings like ataxia and dysarthria, movement disorders including dystonia, dyskinesia, parkinsonism, and sometimes myelopathy.(10,17). Magnetic resonance imaging (MRI) abnormalities mainly consist of a signal hyperintensity on T1-weighted images in the internal pallidum. It may also be seen in the putamen, the caudate nucleus, the capsula interna, the mesencephalon, and the cerebellum, and is believed to reflect local manganese accumulation(10,17).

Here, we aim to present neurological findings of five patients with liver disease that had cranial MRI findings typical for liver disease and were followed in our Movement Disorders outpatient clinic and discuss the different neurological findings in liver failure and review the literature about neurological and radiological findings in liver failure.

CASE PRESENTATION

Case 1

A 70 year-old male patient with chronic liver failure was referred to our movement disorders clinic for the clarification of the etiology of his tremor. One year ago he recognized bilateral hand tremor while drinking and writing. As the liver function worsened with time, tremor also got worse. But tremor did not involve head or feet. The neurological examination revealed mild bilateral bradykinesia, rigidity and rest tremor predominantly on the left upper extremity and bilateral postural and action tremor of the arms. He did not have cognitive impairment. The severity of liver disease was mild (Child class A). Its cause remained elusive despite the detailed workup. He did not drink alcohol. His past medical history showed hypertension and diabetes mellitus type II. Biochemical investigations did not reveal any other etiological causes of tremor. He underwent cranial MRI which demonstrated hyperintensity on T1-weighted images in the bilateral internal pallidum and cerebrocerebellar atrophy (Figure).

His bilateral action and postural tremor could be accepted as symptoms of essential tremor, but the close fluctuating relationship between the liver dysfunction and tremor arouse the etiologic possibility of chronic liver disease as the cause of tremor. Since he had bilateral symptoms early in the course suggesting extrapyramidal disease other than idiopathic Parkinson disease and accompanying imaging findings without any other possible cause, the symptoms were ascribed to result from chronic liver disease. Since his symptoms and signs were mild, we decided to follow up the patient with a watchful-waiting strategy while he was having treatment for liver disease. At six month follow-up, there was no progression or improvement of either liver function or tremor.

Case 2
A 73-years-old female patient with acute myeloid leukemia (AML) and liver cirrhosis secondary to hepatitis C virus (HCV) infection and portal vein thrombosis admitted to our outpatient clinic complaining about progressive forgetfulness and disequilibrium for six years. She has been treated with donepezil 5mg/day for 1 year. Her past medical history revealed arterial hypertension, diabetes mellitus type II with poor glycemic control, distal symmetrical polyneuropathy secondary to DM and cardiac arrhythmia. Neurological examination demonstrated dysmetria of right upper extremity and impairment of executive functions and memory. She was investigated for other reasons of extremity ataxia and cognitive impairment without any findings. Since she had cranial MRI findings showing bilateral hyperintensity in the internal pallidum and thalamus on T1-weighted images, her symptoms were ascribed to chronic liver failure.

Case 3

A 48 year-old female patient admitted with complaints of transient amnesia episodes, tremor and imbalance. She had history of antiphospholipid syndrome. Neurological examination revealed mild resting and severe postural tremor predominantly on the right hand, bradykinesia, bilateral synkinesis, rigidity, slow saccadic eye movements, cerebellar dysarthria, difficulty on tandem walk, globally brisk deep tendon reflexes. She had cognitive impairment with mini mental examination score of 22/30. She also had multiple and widespread petechia on skin, splenomegaly, prolonged prothrombin time and INR. Movement analysis by polymyography showed 5-6 Hz, regular, rhythmic tremor activity. Electroencephalography demonstrated generalized irregularity without any epileptiform activity. Increased signal intensities on T1 weighted images on cranial MRI with biochemical investigations indicating impaired liver functions and abdominal computed tomography showing decreased caliber of portal vein and abnormal congestion of splenorenal and retroperitoneal veins led to the diagnosis of portal vein thrombosis which was probably related to the antiphospholipid syndrome, portosystemic shunt and secondary neurological findings. Since she had fluctuating cognitive impairment, ataxia, resting and postural tremor and other parkinsonian findings like bradykinesia and rigidity in the presence of neuroimaging findings which are commonly seen in chronic liver failure, she was diagnosed as AHCD.

Case 4

A 45 year-old male patient with chronic liver failure for 10 years admitted with mild progressive slowness and hoarseness which existed for a year. He had rigidity, difficulty on tandem walk, globally brisk deep tendon reflexes, dysdiadochokinesia and dysmetria on neurological examination. Dysdiadochokinesia and dysmetria were predominant on the right side of the body. Liver disease was mild (Child class A). Cranial MRI demonstrated hyperintensity of the bilateral putamen, diencephalon and subthalamic nucleus on T1-weighted images. As subacute and progressive neurological symptoms paralleled the liver disease in the presence of supportive MRI findings, they were attributed to the chronic liver disease.

Case 5

A 50 year-old female patient with diagnosis of chronic liver failure due to chronic intrahepatic cholestasis and intermittent hepatitis was admitted to our clinic. She complained of progressive slowness of her left hand and foot. She had previous history of hypothyroidism. Neurological examination revealed mild bilateral action and postural tremor and bradykinesia predominant on the left hand, and hypomimia. Axial and extremity rigidity, dominating the left side was detected. Neither sleep disorders nor autonomic dysfunction were found. Cranial
MRI demonstrated minimal cerebellar atrophy and T1-hyperintensities of bilateral internal pallidum. Serum analysis showed cholestasis, negative antimitochondrial antibodies (AMA) and normal ceruloplasmin level. Liver biopsy showed hepatitis, mild cirrhosis, copper and iron deposition. She got benefit from treatment with levodopa and dopamine agonists. We followed the patient for 8 years and observed a slowly progressive course. All clinical and radiological findings are shown in Table.

**Figure 1:** Cranial MRI showed hyperintensity on T1-weighted images bilateral in the internal pallidum.

**Table** Overview of clinical and radiological findings reported in the text

<table>
<thead>
<tr>
<th>Patient</th>
<th>Concomitant disease</th>
<th>MRI: T1 hyperintensity</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/m/70</td>
<td>HT, DM II</td>
<td>GP I</td>
<td>tremor (R,A,P)</td>
</tr>
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<td></td>
<td></td>
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<td>rigidity</td>
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<td>GP I, STN, Putamen</td>
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<td></td>
<td></td>
<td></td>
<td>Thalamus</td>
</tr>
<tr>
<td>2/f/73</td>
<td>AML, HCV, DM II, HT, PNP</td>
<td>x</td>
<td>Ataxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Frontal-lobe dysfunction</td>
</tr>
<tr>
<td>3/f/48</td>
<td>APS</td>
<td>x</td>
<td>Dysarthria gait dysfunction</td>
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<td></td>
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<td>Dysmetria</td>
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<td></td>
<td>Dysdiadochokinesis</td>
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<tr>
<td>4/m/45</td>
<td></td>
<td>x</td>
<td>gait dysfunction</td>
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<td></td>
<td></td>
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<td>MCI</td>
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<tr>
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<td>x</td>
<td>tremor (A,P)</td>
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<td></td>
<td></td>
<td></td>
<td>rigidity</td>
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<td>bradykinesia</td>
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</tbody>
</table>

GPI, globus pallidus internus; STN, subthalamic nucleus; m, male; f, female; HT, hypertension; DM, diabetes mellitus; R, resting; A, action; P, postural; AML, acute myeloid leukemia; HCV, hepatitis C virus infection; PNP, polyneuropathy; APS, antiphospholipid syndrome; MCI, mild cognitive impairment
DISCUSSION

In this report, we present various neurological findings in patients with liver disease having MRI findings which are commonly attributed secondary to the liver disease, possibly AHCD. AHCD exhibits a great variety of neurological symptoms and is not restricted to parkinsonism which is emphasized at most. Clinical findings in AHCD are neurocognitive involvement, hyperkinetic or hypokinetic movement disorders and myelopathy. Patients may exhibit acute encephalopathy presenting with delirium episodes or may have more insidious chronic course initiating with apathy and lethargy or aggression and hyperactivity progressing to dementia and behavioral disturbances. Movement disorders seen in this context are tremor or flapping tremor, parkinsonism, chorea, myoclonus and dystonia\(^{(10,17)}\). Symptoms related to cerebellar involvement are also reported and are limb and gait ataxia, and saccadic eye movements\(^{(11,15)}\).

The first case shows features of parkinsonism including tremor, rigidity and bradykinesia. Taken together with bilateral hyperintensities in the internal pallidum on MRI this is a typical example of AHCD as described in the literature\(^{(3,4,14)}\). Hyperkinetic movement disorders were previously reported in AHCD\(^{(9)}\). Although he firstly developed tremor during posture and action, at the time we examined him, he had symptoms of parkinsonism. Resting tremor and the asymmetry of signs are also typical of Parkinson's disease. This clinical status without the evidence of liver failure may suggest the diagnosis of essential tremor which progressed to Parkinson's disease. However, absence of family history of tremor, late onset development and timing in close relation with liver failure suggest that this tremor is probably secondary to the liver failure. Additionally, the major diagnostic tool in this case is the presence of MRI findings. The second case highlights the broad spectrum of clinical findings in AHCD. The patient has rightsided ataxia and frontal lobe dysfunction, but no signs of parkinsonism, which may suggest several degenerative, structural or metabolic diseases and were also described in AHCD\(^{(9,17)}\). Likewise imaging results are supportive for AHCD. Ataxia is a known sign in the course of AHCD\(^{(11)}\). But compatible T2 signal abnormalities of cerebellum or brainstem which were previously described\(^{(11)}\) could not be shown in our patients with ataxia. However, we should keep in mind that all neurological symptoms do not always have related MRI findings which may partly be attributed to the quality of scans and presence of required special sections. Case 4 also represents combination of cerebellar and extrapyramidal findings with neuroimaging findings confined to basal ganglia. In the course of cirrhosis, cognitive deficits were previously reported to involve visuospatial tasks. Specifically, tests sensitive for visual search and sequencing were impaired\(^{(17)}\). Therefore, authors concluded that neuropsychological profile should be assessed to justify the underlying insult as the liver disease in dementia. Our case 2 predominantly had memory impairment keeping in mind her age, cognitive problem may be secondary to a degenerative dementia. Asymptomatic cases with incidental T1 hyperintensities are possibly encountered in the course of liver failure. Nevertheless, co-occurrence of ataxia and cognitive impairment without any other metabolic and vascular reason lead to the assumption that those findings are related to liver disease rather than any other degenerative disorder.

Neurological picture in AHCD is suggested to be related to toxic metabolite deposition in brain tissue and correlates with manganese blood levels\(^{(7,8)}\). Toxic metabolites bypass the liver by the way of portosystemic shunts developing in cirrhotic liver disease and reports
suggesting existence of portosystemic shunts and not declining liver function as the major risk factor in the development of AHCD\(^5,16\) support this observation. Therefore, portosystemic shunts without the evidence of liver failure may lead to similar symptomatology as seen in our Case 3. Portal vein thrombosis leads usually to variceal formation and thus porto-systemic shunting, which is conversely debated to be the main reason for AHCD\(^2,8\).

Considering all those above mentioned different clinical entities showing diverse neurological and systemic findings, neuroimaging may be the key supportive tool for the etiological diagnosis of the neurological symptoms of AHCD. Magnetic resonance imaging (MRI) abnormalities mainly consist of a signal hyperintensity on T1-weighted images in the internal pallidum\(^4,8,13\). Hyperintensity may also be seen in the putamen, the caudate nucleus, the capsula interna, the mesencephalon, and the cerebellum. Cerebellar atrophy is, to our knowledge, not described to be associated with AHCD. But we may speculate that it could be the long term result. Association between the location of T1-hyperintensities and clinical signs is not obvious. Furthermore, T1-hyperintensities are characteristic for AHCD but not specific\(^{12,1}\). Therefore, diagnosis should not be done only based on imaging findings. Wilson's disease should be considered in differential diagnosis as its clinical presentation and imaging findings can be confusingly similar\(^{11}\). Hyperintensity of internal pallidum on T1-weighted images were detected in 52-100% of patients with chronic liver failure\(^{12}\), despite the rarity of AHCD. Definite diagnosis may require neuropathology to differentiate from other degenerative diseases.

Abnormal hyperintensity is believed to reflect paramagnetic substance deposition, specifically local manganese accumulation\(^{10,17}\). Manganese accumulation might not be the only factor involved in the pathogenesis of AHCD. Focal spongiform abnormalities, changes of water content and myelinolysis due to systemic osmotic changes may also play role.

As we do not have neuropathology which is a limitation of our presentation, we cannot conclude the diagnosis as definite AHCD. Moreover, the presented patients represent a sample from the movement disorders outpatient clinic, probably not covering whole aspects of neurological findings in AHCD. However, this report still shows the combinations of different neurological symptoms in AHCD. On the other hand, suspicion of liver disease or portosystemic shunts should be kept in mind in patients before diagnosing any neurodegenerative disease and giving treatments toxic to the liver since neurological symptoms may occur in the presence of normal liver enzymes. Lastly, diagnosis of neurological disorders developed in the course of liver disease or co-occurred with liver disease requires a detailed evaluation and liver disease may lead to any neurological symptom or sign.

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