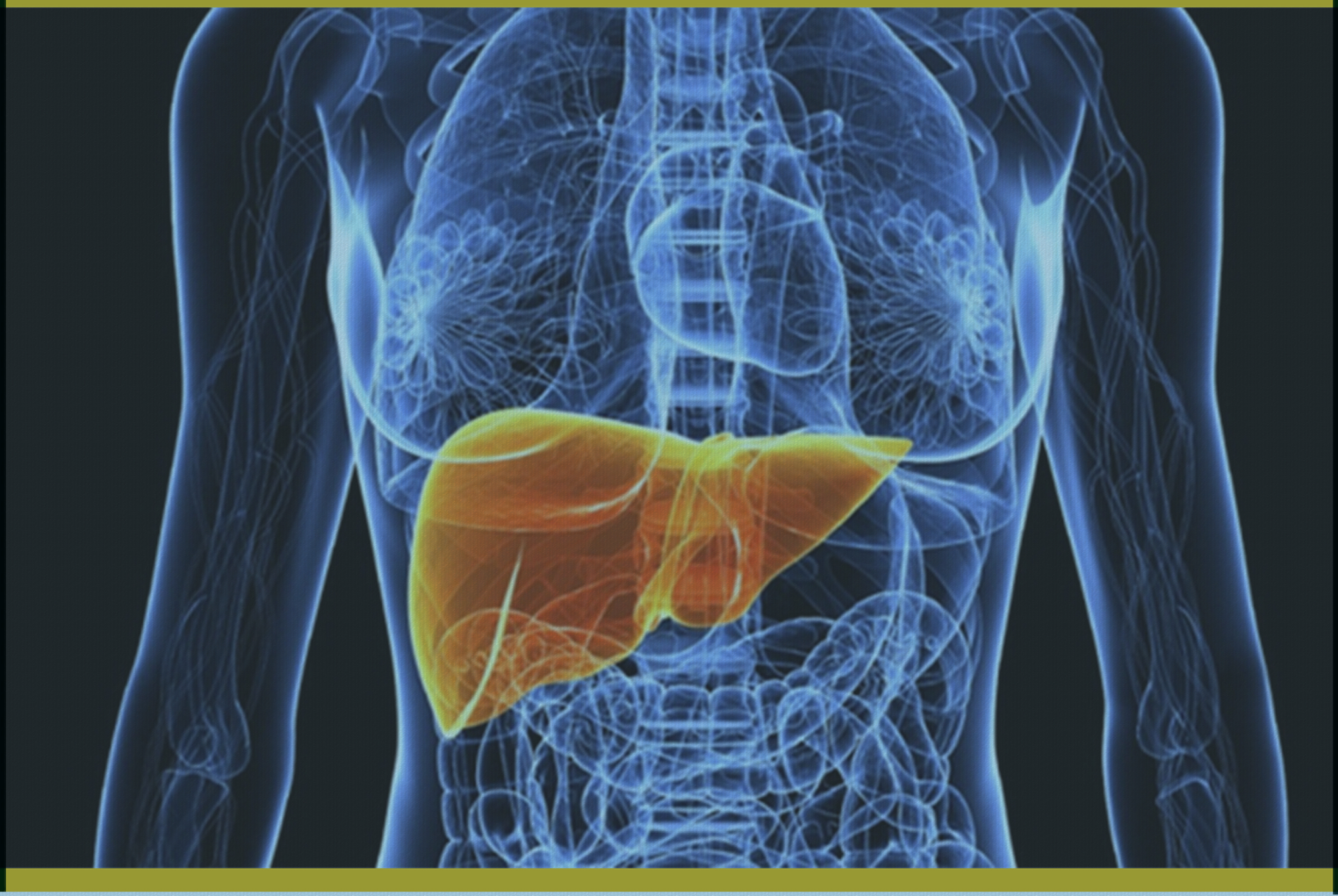
August, 2015 ● Volume 1, Issue 2

Openventio PUBLISHERS

ISSN 2379-4038

LIVER RESEARCH

Open Journal



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ISSN 2379-4038 Open Journal Volume 1, Issue 2

Preface to the Second Issue

In this issue of Liver Research - Open Journal, we have a wide variety of articles that would interest the clinical hepatologist and researcher alike. The review on hepatitis C treatment impact on health care systems in the US will have resonance amongst clinicians worldwide whether they are working in primarily state funded or privately funded health care setups. In a comprehensive review, the role of bile acid activated Farnesoid X Receptor (FXR) in promoting lipid oxidation, reducing inflammation and fibrosis in the liver is discussed. Clinicians and researchers are offered a clear and well-referenced paper here. Siqueira offers a short review on NASH and cardiovascular risks for a wide audience of clinicians who might include cardiologist, diabetologists as well as the general hepatologist. This issue rounds up with a fascinating case of hepatic myelopathy.

H. H. Tsai, MD, FRCP
Editor-in-Chief
Liver Research - Open Journal

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ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-e002

Editorial

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Volume 1 : Issue 2
Article Ref. #: 1000LROJ1e002

Article History:
Received: June 30th, 2015
Accepted: June 30th, 2015
Published: June 30th, 2015

Citation:
Tsai HH. Magnetic resonance elastography comes of age. *Liver Res Open J*. 2015; 1(2): e4-e5.

Magnetic Resonance Elastography Comes of Age

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Clinicians are always in search of a less invasive method of diagnosing and assessing a patient. Patients with liver cirrhosis are no exception. Liver cirrhosis is the end stage of many liver pathologies and knowledge of the onset and stage of liver cirrhosis is important to the clinician as it dictates the treatments on offer. This has become increasingly important in viral hepatitis, as it determines level and timing of anti-viral therapy. Furthermore, onset of cirrhosis would alert the physician to screen for varices and hepatocellular carcinoma. To date the gold standard for diagnosing and staging liver cirrhosis is percutaneous liver biopsy. This is expensive and carries a significant complication rate and a small mortality rate. There could also be sampling error and it only shows if the area targeted has the cirrhotic changes, and does not give the picture of the entire liver. There have been attempts at non-invasive tests like the Fibrotest and ultrasound based elastography. There are at least two methods of ultrasound based elastography. Deformation elastography depends on the constant pressure/stress applied to the organ and shear wave elastography in which a shear wave is applied and propagation measured. These measures are at best qualitative and has a disadvantage of being operator dependent and subjects who have small livers or prominent fat cover may be difficult to assess.[1]

Magnetic Resonance Elastography (MRE) was first described in 1995. Since then the technique has been refined and applied to the liver. The technique uses propagating mechanical shear waves. The waves propagate more quickly in stiffer tissue. Wave propagation depends on wavelength, so the stiffer the tissue, the lower frequency (longer wavelength) is required to propagate the wave a given distance. A wave generator is applied to the liver at a frequency range of between 20-200 Hz. Imaging is done in one or more breathe holds and wave images taken. Special software generates elastograms that quantitatively display the tissue stiffness which can be displayed numerically or as colour-coded overlay on the Magnetic Resonance Imaging (MRI) images. (Figure 1)

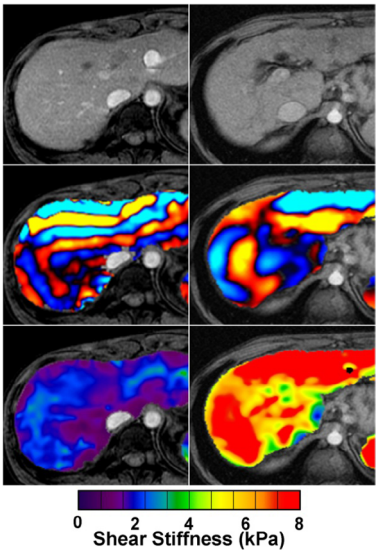

Figure1: Normal liver is pictured on the left and the cirrhotic liver on the right. The top image is the MRI scan, the second row show the shear wave signal and the third, the integrated shear stiffness in kPa, colour coded as shown.

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-e002

These images have proved valuable to the clinician. They tell the clinician of the stiffness and by implication degree of cirrhosis but more than that they show whereabouts the stiffness is. Biopsy samples only capture the histology of the targeted area and are open to sampling variability. MRI elastography gives the whole picture of what the liver is like.

Two recent papers have demonstrated the superiority of MRI elastography over fibrotest and ultrasound based elastography for non-alcoholic fatty liver disease and for all liver diseases including viral hepatitis.[2,3] To date, staging of liver fribrosis/cirrhosis is based on histology. The reproducibility of MRI elastography may sway clinicians to use this in the future as a measure of liver stiffness rather than the more invasive and hazardous method of tissue sampling.

In the first paper, Singh, et al. performed a meta-analysis of data from 12 retrospective studies, comprising 697 patients who had both MRE and liver biopsies performed. 47.1% were with hepatitis C. Overall, 19.5%, 19.4%, 15.5%, 15.9%, and 29.7% patients had stage 0, 1, 2, 3, and 4 fibrosis, respectively. The overall rate of failure of MRE was 4.3%. Based on a pooled analysis of data from individual participants, MRE was shown to have a high accuracy for the diagnosis of significant or advanced fibrosis and cirrhosis, independent of Body Mass Index (BMI) and etiology of Chronic Liver Disease (CLD).[2]

In the second study, Cui,et al. compared the diagnostic utility of 2D-MRE against that of eight Clinical Prediction Rules (CPRs) (AST:ALT ratio, APRI, BARD, FIB-4, NAFLD Fibrosis Score, Bonacini Cirrhosis Discriminant Score, Lok Index and NASH CRN model) for predicting advanced fibrosis in a prospective cohort with paired liver biopsy as the gold standard. A prospective study of 102 patients (58.8% women) with biopsy-proven NAFLD, 2D-MRE and clinical research assessment within 90 days of biopsy. Receiver operating characteristic (ROC) analysis was performed to assess the performance of 2D-MRE and CPRs for predicting advanced fibrosis. In head-to-head comparisons using the DeLong test, 2D-MRE had significantly better AUROC ($P<0.05$) than each CPR for predicting advanced fibrosis. They concluded that compared to clinical prediction rules, 2D-MRE provides significantly higher accuracy for the diagnosis of advanced fibrosis in NAFLD.[3]

Are there drawbacks? It may be perceived as expensive but it is likely to be cheaper than histology. The additional equipment of the wave generator is perhaps the only other outlay if the MRI is already available in the institution. This new modality and how best to use it is still being explored and as it becomes increasingly used by mainstream hepatologists it is likely to be an important tool to the clinician.

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Openventio PUBLISHERS

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-105

Review

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Volume 1 : Issue 2
Article Ref. #: 1000LROJ1105

Article History:
Received: May 6th, 2015
Accepted: May 11th, 2015
Published: May 11th, 2015

Citation:
Khallafi H, George N, Qureshi K. The prescribers' dilemma: treatment of hepatitis c infection for medicaid insured patients in united states. *Liver Res Open J*. 2015; 1(2): 26-31.

The Prescribers' Dilemma: Treatment of Hepatitis C Infection for Medicaid Insured Patients in United States

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ABSTRACT

Introduction of Direct Acting Antivirals (DAA) to Hepatitis C Virus (HCV) treatment armamentarium has offered a great boost to the providers' confidence to safely and effectively treat HCV infection in the majority of patients. However, the cost of these medications is high and thus access is poor. Medicaid insurance providers have devised stringent eligibility criteria to approve the cost of DAA for its members. We reviewed the criteria among various Medicaid agencies from States of Ohio and Pennsylvania and noticed similarities and differences among them. The prerequisite process demanding clinical, laboratory, radiologic or histologic documentation is quite cumbersome and sometimes confusing. In certain aspects the eligibility requirements for DAA are not in concordance with the clinical evidence provided by the recently updated guidelines. We have addressed the dilemma most of the providers face while planning HCV treatment for the Medicaid insured patients in regards to the needed testing, clinical documentation and liver fibrosis assessment, along with the clinical implications of such requirements. While HCV remains a major public health issue, variable State Medicaid policies may lead to disparity in access to the emerging DAA with subsequent healthcare outcomes. These gaps may compromise long term efforts of the public health HCV initiatives.

KEYWORDS: Chronic hepatitis C infection; Direct antiviral medications; Medicaid insurance; Affordable Care Act (ACA).

INTRODUCTION

It is estimated that 3.5 million people living in the United States (US) are exposed to chronic Hepatitis C Virus (HCV), with many cases remaining to be diagnosed.[1] The 2013 United States Preventive Services Task Force (USPSTF) recommends a onetime screening for HCV infection in adults born between 1945-1965 based on evidence indicating proven benefits of chronic HCV treatment in the reduction of all-cause mortality, cirrhosis, hepatocellular carcinoma and potential public health benefit in reducing transmission rates.[2] Previous curative therapies with interferon based regimens were difficult in terms of long length of treatment and numerous side effects with only mediocre treatment outcomes.

In the current era of Direct Acting Antivirals (DAA) for chronic HCV treatment, management guidelines have been created by the Infectious Diseases Society of America (IDSA), American Association for the Study of Liver Diseases (AASLD) and the International Antiviral Society–USA (IAS–USA), to keep up with the pace with which new HCV medications are being released.[3] However, the benefits of these new treatments may be offset by the limited num-

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-105

ber of patients having access to antiviral treatment, based both on insurance status and cost. It is recognized that chronic HCV patients are less likely to be insured compared to patients without this chronic illnesses. Given the recent advent of the Affordable Care Act (ACA) "ObamaCare", the increasing number of uninsured patients will drop from 18% to 13.4% towards the end of 2015.[4] The major concern about cost of treatment has led the State governments to apply restrictive access requirements with complex and burdensome associated utilization management. In addition, the insurance-driven approval of HCV medications, particularly for patients with Medicaid restricted formularies, may further affect patient care and access to treatment, thereby placing additional limitations on physician treatment options.

METHODS

In this study, we sought to determine the HCV treatment coverage policies for DAA in Medicaid insured population. Table 1 depicts some of the salient clinical characteristics and eligibility criteria the insurance agencies are requesting for HCV medication approval. We composed a list of the Medicaid insurance carriers in the States of Ohio and Pennsylvania. Requests were then made to these insurance agencies to provide selection criteria used to determine patient candidacy for DAA therapies for HCV. In addition, HCV medication denial letters were also reviewed to further determine selection criteria.

FINDINGS

The Medicaid insurance coverage for DAA therapy for HCV infection across two States, Ohio and Pennsylvania, have certain similar features, but also differing requirements for medication approval (Tables 1 and 2). Inconsistency in timing of the requested blood work prior to submission of authorization is seen across insurances, ranging from 30 days to 6 months. HCV viral load testing is time sensitive for some insurance providers; however, no clear guideline regarding the timing of the viral load prior to initiation of treatment has been established. A complete laboratory workup to exclude other causes of liver disease is requested by most of the insurance companies. The documentation of the patient's interferon ineligibility, NS3 Q80K polymorphism screening for genotype 1a, HIV status, TSH, uric acid, direct bilirubin, Hepatitis B serology, and ANA are required by some insurances. Interestingly, EKG is requested in patients with known cardiac disease by a few insurance providers. Abdominal imaging is requested to look for hepatocellular carcinoma in cirrhotic patients. Presence of severe or uncontrolled co-morbidities excludes a member from coverage of DAA by certain providers. Documentation of life expectancy is often requested in order to further assess the prognosis and health conditions.

Clear description of psychosocial status of the patients is consistently required by all Medicaid providers across both states and is a constant reason for the delay in medications. Documentation of psychiatric disorders, past or present is required by most of the insurances, with some providers requiring notes from a psychiatrist documenting control of illness with treatment and follow up plans. In patients with known history of alcohol or substance abuse, documentation of last illicit drug and alcohol use is universally required among insurances. Along with that, most providers are requiring negative drug screens within 30 days to 6 months prior to treatment. Some insurance providers are currently offering and mandating enrollment in the HCV adherence program prior to the approval of DAA to certain members, a completed consent document indicating the adherence to HCV regimen often requested.

Medicaid programs necessitate evaluation of extent of the liver disease and fibrosis as a part of HCV treatment approval process. So far, all insurances require documentation of advanced liver disease (stage 3 and 4) prior to approval of medications. There is a high variability among insurance programs in regards to the modality used to assess liver disease. Liver biopsy is the gold standard for staging of fibrosis and it is accepted by all of the insurance providers as a documentation of the stage of liver disease. Non-invasive methods for fibrosis staging that may include Fibroscan, Elastography, Fibrosure test, or Hepascore testing are variably requested by different insurance providers. Only a few programs would accept the clinical documentation of presence or absence of advanced liver disease. The criteria of advanced liver disease is down staged by a few insurance providers in HIV/HCV co-infected patients where they qualify stage 2 or above for DAA approval in such co-infected patients.

DISCUSSION

Based on a recent review and meta-analysis, it is estimated that only 50% of the patients believed to be exposed to HCV infection are screened, 43% have access to outpatient care, 27% have HCV infection confirmed with a viral load testing, 17% undergo liver fibrosis assessment by one of the methods, 16% are prescribed treatment, and only 9% achieve Sustained Virologic Response (SVR).[1] These findings are bound to change with the recent introduction of the Affordable Care Act (ACA) combined with the advent of novel DAA which have significantly higher SVR. The combined effect of availability and access of these drugs to more patients will dramatically change the healthcare and HCV landscape. ACA has improved access to healthcare coverage and offers a significantly broad access to HCV care by covering for screening, diagnosis and, in the most part, treatment of HCV. Both the USPSTF and CDC recommend one-time screening for HCV infection in the general population born from 1945 to 1965 in addition to continuing the recommendation for screening individuals at high risk for HCV.[2] Under the provisions of the ACA, HCV screening is a covered service, which will improve the identification of HCV patient in the lower income individuals, as HCV is found to be more prevalent in this population.[5] Many of the States are expanding Medicaid eligibility under ACA provisions. The rise in the number of individuals with insurance coverage has subsequently increased the number of patients diagnosed with HCV. Although ACA has provided significant opportunities in regard to Hepatitis C man-

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-105

Medicaid Plan	Physician-Patient Contract or a Compliance Program	Documentation of alcohol/illicit substance abstinence	Drug screen	No coverage for decompensated liver disease (child puth class B or C)	Medical history with documentation of psychiatric disorders	Pregnancy test required	Required labs (CBC, LFT, INR, GFR) Detectable HCV RNA levels in serum	Liver biopsy or Fibroscan required (Fibrosure not accepted)	Evidence of fibrosis stage 3-4 or HCC meeting Milan criteria without HIV co-infection	Evidence of fibrosis stage 2 or more with HIV co-infection	Serious extra-hepatic manifestations of HIV infection	Estimation of patients life expectancy	Interferon ineligibility	Authorization period limitation
1		X	X	X		X	X		X				X	
2		X	Within 30 days	X		Within 30 days	Within 30 days	X	X				Within 30 days	Reauthorization on every 6 weeks
3		X	Within 90 days	Coverage only if managed by liver transplant center			X		X	X	X		X	
4		6 months documented soberity					X		X			X	Reauthorization on after initial 8 weeks required	
5		30 days prior to treatment		X			X		X				X	
6	Health plan's HCV Adherence Program	Attestation form physician is required confirming abstinence for 6 months and compliance with treatment program participation	Within 30days		X	X	X	Fibrosure accepted but only after reasonable explanation of inaccessibility of Liver biopsy or a Fibroscan	X	x	x		x	
7		X	Within 60 days		X	X	X	X	x			X	X	
8	X	X	X		X		X		"Generally Treat" fibrosis stage 3 or 4				X	

Table 1: Comparison of eligibility criteria.

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-105

Documentation	Requirement
Past treatment History • Outcomes • Interferon Tolerance	Always
Medical History • Complications from HCV and liver disease • Medical co-morbidities • Medications	Always
Psychiatric / Social history • Psychiatric disorders • Substance abuse	Always
Compliance assessment and follow up • Patient – physician contract • Health plan's HCV Adherence program • Psychiatrist assessment	Variable
Life expectancy assessment	Variable
Laboratory assessment • Testing • Timing	Variable
Liver stage assessment • Liver biopsy • Fibroscan / Fibrosure • Clinical assessment	Variable
Evaluation for contraindications to treatment	Always

Table 2: Overview of documentation and requirements.

agement, barriers to access of these HCV treatments still remain. Given the high cost of the medication, State Medicaid programs have substantial discretion with regard to medications coverage and related utilization management.

Review of the insurance agency criteria for DAA treatment for HCV showed apparent differential in Medicaid coverage policies in comparison to privately or Medicare insured patients. Based on the current criteria, Medicaid patients with advanced stages of fibrosis (F3- F4) are more likely to get medications approved, while patients with other insurances provide coverage regardless of the stage of fibrosis. It remains to be determined whether there will be a difference in overall HCV burden and healthcare outcomes in regards to treatment based on the stage of liver disease and the type of insurance. There is growing evidence that HCV cure with the DAA regimens has favourable public health and economic future outcomes in both late and early fibrosis stages, prior treatment history and cirrhosis.[6,7]

Individual Medicaid insurance providers have different criteria for the method to use for fibrosis evaluation. Liver biopsy is the gold standard for fibrosis staging and is universally accepted, while, not all insurance providers allow use and accept the results of other modalities as non-invasive tools of liver fibrosis assessment. From a clinical standpoint, liver biopsy is an invasive technique with associated morbidity. The accurate evaluation of fibrosis using liver biopsy is also complicated by sampling error and inter-observer variation in staging, particularly when inadequate sampling occurs.[8,9] Liver biopsies on a large-scale for staging purposes cannot be a reasonable, cost effective or a practical approach. As a result, non-invasive tools play a major role in assessment of liver fibrosis. The non-invasive approaches include the evaluation of various laboratory parameters which are included in Fibrosure/Fibrotest, or in conjunction with liver stiffness evaluation by Fibroscan, which could obviate the need for liver biopsy with over 86.7% accuracy.[10] However, many medical centers still do not carry the Fibroscan or other liver stiffness measurement tools and are not able to conduct this testing with ease.

As recommended by the guidelines, the rationale of immediate and timely treatment of patients with advanced fibrosis,[3] comes from numerous clinical and populations studies and is generally accepted by Medicaid.[11,12] Populations at higher risk for liver disease progression, Metavir F2, co-infection populations (HIV, Hepatitis B), those with coexistent liver disease (NASH or alcoholic) and patients with extra hepatic manifestations are not regularly listed in the Medicaid initial treatment considerations criteria. Those populations should be prioritized as per expert recommendations.[3] In particular, those patients with severe extra hepatic manifestations, such as Type 2 or 3 essential mixed cryoglobulinemia with end organ manifestations, have been shown to respond to immediately to treatment with appreciable benefits reduced mortality rates.[13,14] These criteria are not yet adopted by most of the Medical programs.

Treatment of individuals at high risk to transmitting HCV is a major public health opportunity that may yield long-term future benefits. For example, there are no Medicaid program criteria that addresses HCV infected women of childbearing age. It is estimated the risk of HCV vertical transmission from HCV RNA positive women who are HIV negative at 5.8% and among HIV-positive women at 10.8%.[15] There are discriminatory criteria with respect to persons who inject drugs (PWID)

as proof of abstinence of drugs is regularly requested by Medicaid programs.[16] On the other hand, the guidelines suggest that PWID should be considered for HCV treatment.[3] The experience of some European countries has shown that access of PWID to HCV therapy (including DAA) and scaling up HCV treatment is feasible using an integrated multidisciplinary approach.[17-19]

The need for psychiatric evaluation is enforced by most of the Medicaid providers. This requirement is implemented for anyone who has used illicit drugs, or any psychotropic medication in their lifetime. The DAA do not have any significant psychiatric side effects. DAA does not induce or exacerbate any psychiatric illness and thus there is no evidence behind the need for psychiatric evaluation or follow up of HCV patients while on treatment. Medicaid program use this requirement to ensure that patients will show compliance and understand the illness better if they will have a psychiatrist visit. This eligibility requirement has generated visits to psychiatrists and also delays the initiation of treatment. In addition the requirement of negative screening for drugs or alcohol is required by most of the providers as a marker or compliance and understanding of patients' abstinence for and while on the treatment. The timing of the drug and alcohol screen varies from 30 days to 6 months among different Medicaid providers. A few health plans have formulated HCV Adherence programs, which requires enrollment by a phone call. These programs are meant to provide education and counselling in regards to compliance. Those programs are mandating the members to enroll for the approval of medications. The utility of such requirement still needs to be elucidated.

There are differences within Medicaid programs not only within a State but also between other States in regard to the required clinical documentations and testing as well as timing of these tests. Several of the blood tests which are included in the eligibility criteria do not have strict clinical evidence in regards to efficacy of DAA. Insurance companies require testing for Uric Acid, TSH or NS80K Polymorphism. These tests were needed with interferon based therapies or first generation protease inhibitors and do not have any evidence in regards to side effects or efficacy of current DAA. In addition, the Medicaid driven HCV medications, the locally approved restrictive formularies may also affect patient care and access to treatment thus limiting physician HCV treatment options and choices. Those additional requirements subsequently result in burdensome and increasingly complex pre-authorization and appeal forms especially in the rapidly evolving DAA. Though, the use of interferon is outdated in this era of DAA but still some insurance providers are requesting the documentation of reasons of interferon in-eligibility; which seems completely unnecessary as no one should be using interferon based regimens.

Certainly HCV treatment is becoming relatively easy in regards to the pill burden and medical management while on treatment. However, approval process is a daunting task, which is requiring considerable amount of time, resources and manpower. Some insurance providers are limiting the DAA to the prescriber's specialties (hepatology, gastroenterology, infectious diseases and transplant physician). As the number of patients screened for HCV continues to increase, the provider workforce will lack the capacity to provide care for all the newly diagnosed HCV patients in need or wishing to be treated. Limiting DAA to certain prescribers may compromise public efforts to expand access to HCV treatment especially in the rural areas where the primary care clinics as the cornerstone of a "test-and-treat" approach to hepatitis C.[20,21]

CONCLUSION

In summary, it is indeed a very exciting time for the management of HCV infection. The convergence of the ACA with the advent of novel DAA has created new opportunities for HCV management but has also created challenges that affect various populations. As we bring increasing number of newly insured patients and these DAA into our practices, several barriers to treatment in the Medicaid population will arise. While Medicaid programs face the high cost of the emerging HCV drugs and thus implementing restrictive policies, the medical providers are trying to adjust and acquaint with those requirements. Collaborative efforts are required to further optimize and better foster access to HCV care which can only be accomplished by balancing ethical questions, evidence based data and public health goals.

CONFLICTS OF INTEREST: None.

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ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-106

Review

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Volume 1 : Issue 2
Article Ref. #: 1000LROJ1106

Article History:
Received: May 3rd, 2015
Accepted: June 10th, 2015
Published: June 10th, 2015

Citation:
Khalid Q, Bailey I, Patel VB. Non-Alcoholic fatty liver disease: the effect of bile acids and farnesoid X receptor agonists on pathophysiology and treatment. *Liver Res Open J.* 2015; 1(2): 32-40.

Non-Alcoholic Fatty Liver Disease: The Effect of Bile Acids and Farnesoid X Receptor Agonists on Pathophysiology and Treatment

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is an emerging epidemic in light of its two predisposing factors, a surge in both obesity and diabetes rates with reports of between 70-80% of obese individuals in Western countries. The disease progression of NAFLD remains elusive but is generally attributed to insulin resistance, lipid metabolism dysfunction, altered immune response to name a few. Potential therapeutic strategies should target one or some of these pathological events in the liver, however currently no specific therapies for NAFLD exist. Thus novel therapeutic approaches to manage the chronic liver disease epidemic are becoming essential. In this review we discuss the evidence supporting the role of bile acid activated Farnesoid X Receptor (FXR) in promoting lipid oxidation, reducing inflammation and fibrosis in the liver. We also examine the potential of FXR agonists, as an attractive class of drugs for the safe and effective treatment of NAFLD.

KEYWORDS: Bile acids; Nuclear receptors; Fatty liver disease; Lipids; Cholesterol.

ABBREVIATIONS: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CA: Cholic Acid; CDCA: Chenodeoxycholic acid; CYP7A1: Cholesterol 7α-hydroxylase; CYP8B1: sterol 12-hydroxylase; CYP27A1: sterol 27-hydroxylase; DCA: Deoxycholic acid; LCA: Lithocholic acid; FXR: Farnesoid X Receptor; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; OCA: Obetocholic acid; PXR: Pregnane X Receptor; TNF-α: Tumour Necrosis Factor alpha; TZD: Thiazolidinedione; UCDA: Ursodeoxycholic acid; VDR: Vitamin D Receptor.

INTRODUCTION

Bile acids produced in the liver as an end product of cholesterol catabolism were originally categorised as physiological detergents that facilitated the metabolism of dietary lipids and lipid soluble vitamins (A, D, E and K), and the hepatobiliary secretion of endogenous metabolites and xenobiotics.[1-4] However, recent interest in bile acids over the past few years has shed new light on their roles in both the synthetic and regulatory metabolic pathways, pertaining to lipid, carbohydrate and cholesterol regulation acting as indispensable signalling molecules co-ordinating these network of biological processes.[5]

Whilst bile acids (Chenodeoxycholic acid (CDCA), Deoxycholic acid (DCA), Lithocholic acid (LCA), Cholic Acid (CA)) can negatively feedback their own production,[6] they can also act as endogenous ligands for nuclear receptors to facilitate this regulation.[3,4,7] The nuclear receptor, Farnesoid X Receptor (FXR; NR1H4) was the first bile acid receptor discovered,[8] followed by other nuclear receptors in the NR1I subfamily, namely Constitutive Androstane Receptor (CAR; NR1I3), Pregnane X Receptor (PXR; NR1I2) and Vitamin D Receptor (VDR; NR1I1).[4,9]

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-106

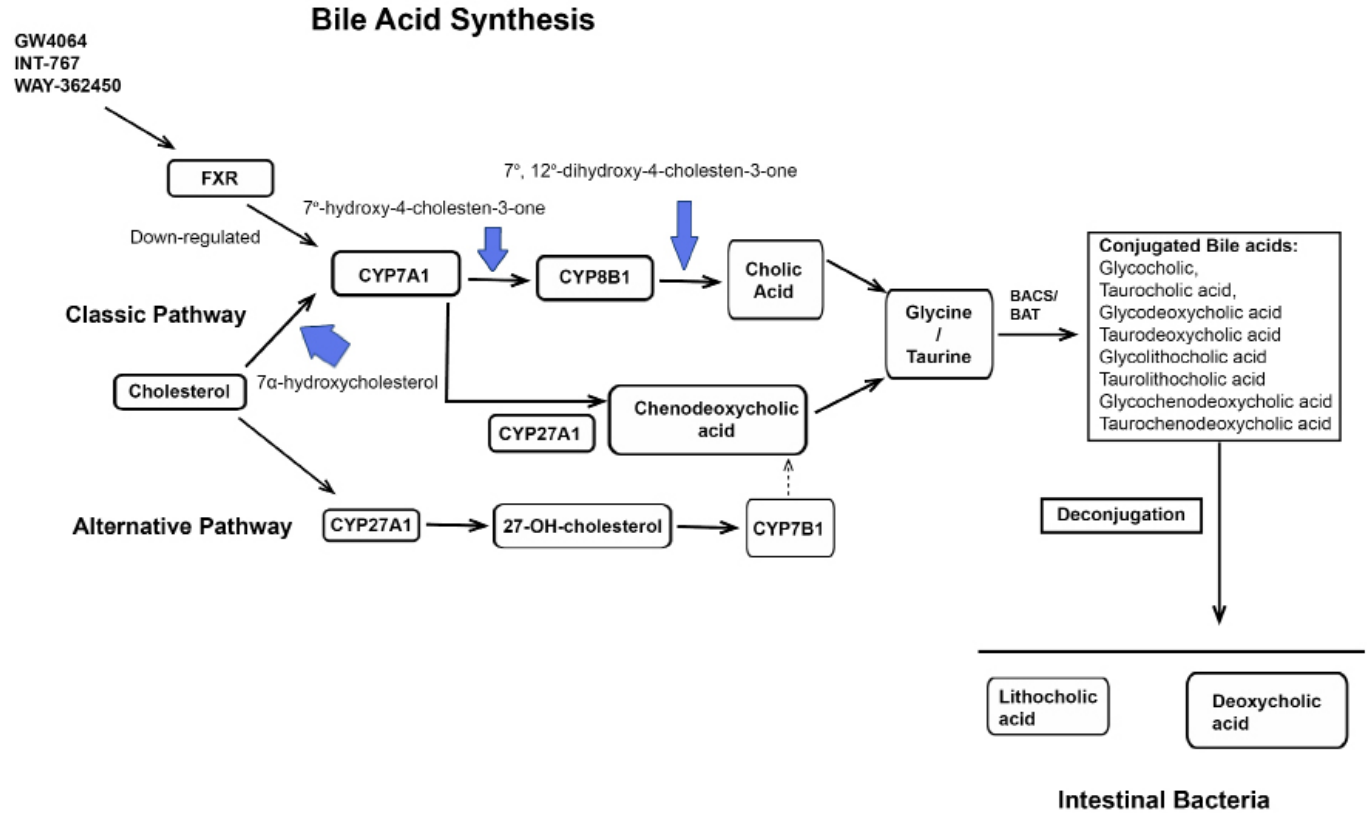
In terms of nuclear receptor activation, PXR and VDR are stimulated by lithocholic acid (EC50 of approximately 100 nM), which is a hydrophobic bile acid derived from the 7-dehydroxylation of CDCA by intestinal bacteria.[2,4] FXR though can be stimulated to varying degrees by most bile acids (CDCA>LCA=DCA>CA), but with the highest potency by CDCA, with an EC50 of approximately 10 μM.[2] Conversely, constitutive androstane receptor is not triggered directly by bile acids but nonetheless is vital for controlling detoxification and transport of bile acids.[10,11] Of all the nuclear receptors, VDR is expressed broadly across different tissue types. However, FXR and PXR are found abundantly, mainly in tissues in direct contact with bile acids for example in the intestine and liver.[2]

FXR is now considered as a "master regulator of bile acid metabolism" as it is involved in all phases of the biosynthetic pathway,[2] affecting gene expression of ileal bile acid binding protein, small heterodimer partner, phospholipid transfer protein, ABC transporters and apolipoprotein C-II.[2,12-14] Activation of these nuclear receptors leads to a reduction in bile acid synthesis, promotion of lipid oxidation, drug metabolism and transport, as well as affecting cholesterol metabolism.[14] Conversely dysregulation of bile acid metabolism has a significant impact on inflammatory and metabolic disorders, such as Non-alcoholic fatty liver disease (NAFLD), diabetes, and obesity.[2,11,15] This review aims to highlight recent advances in bile acid nuclear receptor activation, as well as the therapeutic potential of bile acids and their derivatives for the treatment of NAFLD.

BILE ACID SYNTHETIC PATHWAYS

The metabolism of bile acids is tightly controlled, where approximately 95% of the 3g bile acid body pool that is secreted into the intestine is reabsorbed *via* the enterohepatic circulation, with a small amount excreted in the faeces (200-600 mg/day). Bile acids that are lost are replaced by *denovo* hepatic synthesis[5] derived from cholesterol catabolism (approximately 500 mg).[16]

Hepatic bile acid synthesis begins from cholesterol catabolism involving a 17 step enzymatic pathway.[2,14,16] The synthesis of bile acids is a complex process catalysed by several cytochrome P450 enzymes[2] and involves two major bile acid biosynthetic pathways, the classic and alternative pathway.[4] In the classic pathway, cholesterol is converted to 7α-hydroxycholesterol by the microsomal cytochrome P450 enzyme, Cholesterol 7α-hydroxylase (CYP7A1), which is also



Catabolism of cholesterol produces the primary bile acids Cholic Acid (CA) and Chenodeoxycholic acid (CDCA) through one of two pathways in the liver. Key regulated enzymes in both pathways are shown. In the classic pathway, Cholesterol-7α-hydroxylase (CYP7A1) catalyses the first rate-limiting step to convert cholesterol to 27-hydroxycholesterol. However, sterol 27α-hydroxylase (CYP27A1) initiates the alternative pathway. Oxysterols, such as sterol 7α-hydroxylase (CYP7B1) produced in peripheral tissues are transported to hepatocytes and converted to CDCA and CA in the alternative pathway. CA synthesis is tightly regulated by 7α-hydroxylase (CYP8B1) in the classic pathway. In the intestine, CA and CDCA are conjugated with Glycine (G) or Taurine (T) by the enzymes Bile Acid Transferase (BAT) and Bile acid coenzyme A synthase (BACS). Some conjugated bile acids such as glycocholic acid, taurocholic acid, glycodeoxycholic acid, taurodeoxycholic acid, glycolithocholic acid, taurolithocholic acid, glycochenodeoxycholic acid and taurochenodeoxycholic acidare de-conjugated and subsequently dehydroxylated at the 7α-position by bacterial enzymes and converted to the secondary bile acids, Deoxycholic acid (DCA) and Lithocholic acid (LCA) respectively. Farnesoid X receptor is activated by agonists such as GW4064, INT-767 and WAY-362450 leading to reduced expression of CYP7A1 and lower levels hepatic bile acids.[2,4,5]

Figure 1: Bile acid synthesis.

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-106

the rate-limiting step.[7] In humans, the immediate by product of these pathways are the primary bile acids, Cholic Acid (CA) and Chenodeoxycholic acid (CDCA).[14] The proportion of CA to CDCA synthesised is approximately equal and is regulated by the microsomal enzyme sterol 12-hydroxylase (CYP8B1) (Figure 1). The alternative pathway is carried out by mitochondrial sterol 27-hydroxylase (CYP27A1). This pathway occurs in the liver, macrophages and several tissue types in the body and predominantly synthesise CDCA.[17] The import of cholesterol to the inner mitochondrial membrane, *via* soluble cholesterol binding protein is thought to be the rate-limiting step in the alternative pathway.[18]

Subsequently, bile acids are conjugated to amino acids, typically taurine or glycine *via* the enzymes bile acid transferase and bile acid coenzyme A synthase, with the proportion of glycine to taurine conjugates estimated as 3 to 1.[17,19] Conjugation of bile acids is an important process as it prepares the bile acids for effective detoxification, enhances their amphipathicity and solubility properties, which consequently leads to impermeability to cell membranes and reduced bile acid toxicity. However, some conjugated bile acids are deconjugated in the intestine by anaerobic bacteria converting CA and CDCA *via* 7α-dehydroxylase to the secondary bile acids, Lithocholic acid (LCA) and Deoxycholic acid (DCA), respectively (Table 1). Both of these bile acids are thought to have toxic properties, with DCA causing colon cancer for example.[20] Whilst most DCA is reabsorbed in the colon and LCA is excreted in faeces, around 4% of LCA is transported to the liver where it is conjugated by amidation and sulfation and subsequently excreted into bile. Furthermore, sulfation of hydrophobic bile acids by sulfotransferase 2A1 is a key route for bile acid detoxification.[17,19]

Primary	Secondary	Conjugated
Cholic acid (CA)	Deoxycholic acid (DCA)	Glycocholic acid
Chenodeoxycholic acid (CDCA)	Lithocholic Acid (LCA) Urosdeoxycholic acid (UDCA)	Taurocholic acid Glycodeoxycholic acid Taurodeoxycholic acid Glycolithocholic acid Taurolithocholic acid
		Glycochenodeoxycholic acid
		Taurochenodeoxycholic acid

Main bile acids found in the liver and intestine.[21,22]

Table 1: Principle Bile Acids.

BILE ACID TRANSPORT IN THE ENTEROHEPATIC CIRCULATION

Increased bile acid concentration in the hepatocytes is the driving force of phosphatidylcholine, cholesterol and bile acid transport through the basolateral membrane, and removal of bile acids at the canalicular membrane into the biliary system.[23] Conjugated bile acids are actively transported by the canalicular bile salt export pump and stored in the gallbladder.[24,25] Furthermore, mutations in the bile salt export pump gene leads to progressive familial cholestatic syndrome, with the accumulation of toxic hydrophobic bile acids leading to cirrhosis in some cases.[26] The proportion of these molecules, phospholipids, cholesterol and bile acids is tightly controlled by forming mixed micelles in the bile to (i) boost cholesterol solubility, (ii) decrease bile acid toxicity in the bile duct, and (iii) during digestion facilitate the uptake of nutrients into enterocytes. Excess cholesterol and/or hydrophobic bile salts causes saturated bile accumulation which can consequently lead to the formation of cholesterol gallstones in the biliary system and gall bladder.

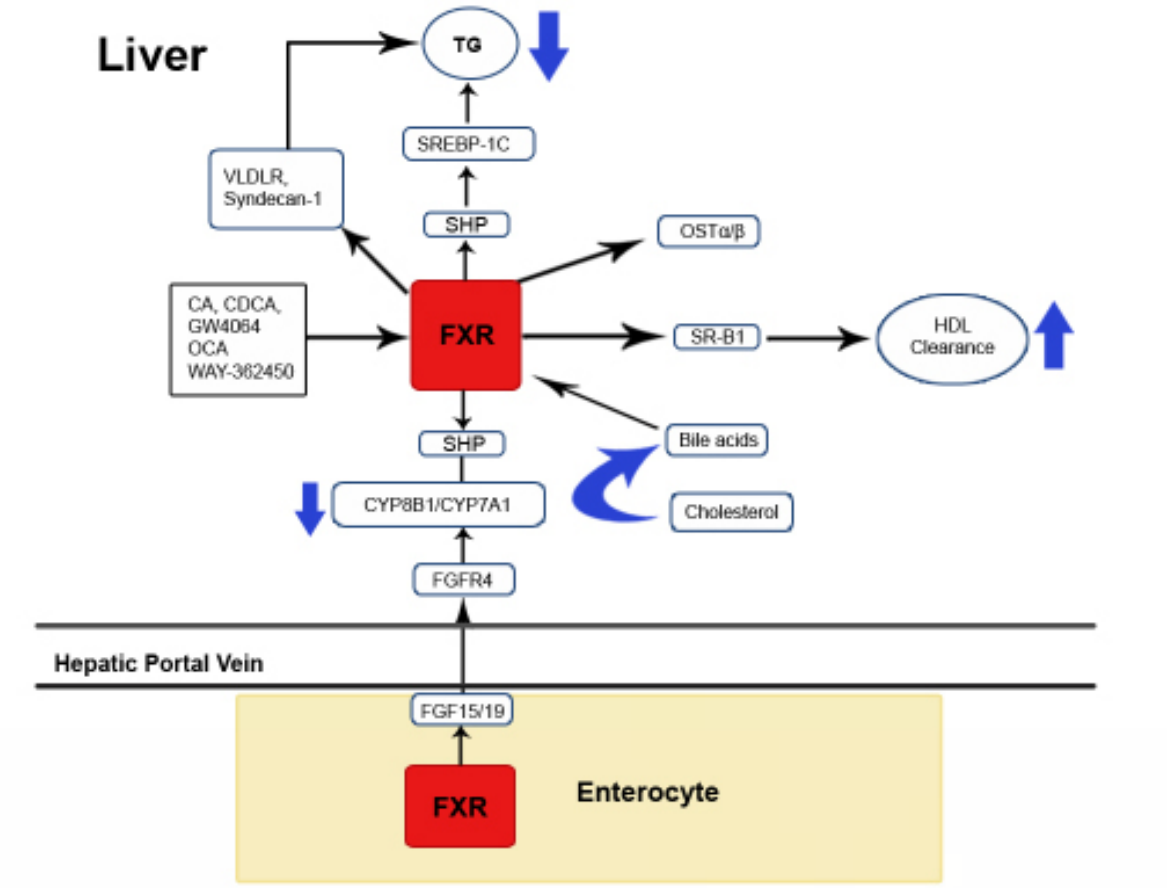
At the brush border membrane of the ileum 95% of bile acids are actively reabsorbed by the sodium dependent transporter. Upon absorption, bile acids bind to the ileal bile acid binding protein and diffuse across the basolateral membrane for release into the blood *via* the heterodimeric organic solute transporters.[27] Completing this cycle, uptake of reabsorbed bile acids to the liver is mediated by Na^+ dependent taurocholate co-transport peptide located in the sinusoidal membrane. Sinusoidal membranes function to efflux bile acids into the circulatory system and therefore express bile acid efflux transporters such as multidrug resistance protein.[4] During cholestasis it has been recognised that these sinusoidal membranes are triggered and could play a fundamental role in the protection of liver injury when bile acids accumulate excessively in hepatocytes.[2] Recent evidence suggests bile acids have the ability to initiate the production of the metabolic hormone fibroblast growth factor 15/19 (FGF-15 in mice, FGF-19 homolog in humans) in the ileocyte through the action of a functional FXR domain. Fibroblast growth factor 15/19 is transported to the liver where it subsequently binds to its cognate tyrosine kinase receptor. This results in the activation of the c-Jun N-terminal kinases 1/2 signalling pathway and down-regulation of CYP7A1 and bile acid synthesis (Figure 2). Interestingly, it is reported that cognate tyrosine kinase receptor β-klotho null mice have raised CYP7A1 mRNA levels and a larger bile acid pool, and that bile acids and cytokines (TNF-α) are also capable of triggering the c-Jun N-terminal kinases 1/2 signalling pathway and as a result down-regulate CYP7A1 Mrna.[28]

THERAPEUTIC APPROACH OF BILE ACIDS FOR NON-ALCOHOLIC FATTY LIVER DISEASE

At present, NAFLD is the most common form of chronic liver disease worldwide and is generally associated with clinical features of the metabolic syndrome.[30] The incidence is significantly increased in diabetics (up to 63%) and in the morbidly obese.[31] Given the epidemic of obesity attributable to the content of fat in modern diet, it is estimated that 42 million children were obese in 2010 and this figure is expected to rise to almost 60 million by 2020.[32] These projections foresee a continued worsening trend in obesity and chronic liver disease, thus alternative therapeutic options are needed.

Generally the spectrum of liver pathology covers ste-

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-106



Bile acids Cholic Acid (CA) and cChenodeoxycholic acid (CDCA) and FXR agonists such as GW4064, OCA and WAY-362450 activate hepatic and intestinal FXR to regulate-genes vital for bile acid metabolism. The activation of hepatic FXR lowers plasma cholesterol and Triglyceride (TG) synthesis via several pathways. For instance Short Heterodimer Protein (SHP)-dependent inhibition of Sterol Regulatory Element Binding Protein-1c (SREBP-1c) leads to the suppression of hepatic TG. Furthermore FXR suppresses bile acid synthesis by reducing CYP7A1 and CYP8B1 expression via SHP. Stimulation of Very Low Density Lipoprotein Receptor (VLDLR) and syndecan-1 also promotes the clearance of TG lipoproteins, and similarly Scavenger receptor class B1 (SR-B1) promotes the clearance of High Density Lipoprotein (HDL) in the liver. In the enterocytes bile acids bind to FXR and as a result elevate the expression of two transporters, organic solute transporter alpha and beta (OSTα, OSTβ) that facilitate bile acid transport into the hepatic portal vein. Induction of intestinal FXR increases the expression of fibroblast growth factor 15/19 (FGF15/19) into the hepatic portal vein. The subsequent binding of FGF15/19 to the hepatic cell-surface receptor fibroblast growth factor receptor 4 (FGFR4) triggers the JNK pathway leading to the suppression of CYP7A1 and CYP8B1 hence a decrease in bile acid synthesis.[3,29]

Figure 2: Overview of FXR regulation.

atosis to the more severe conditions Non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis.[33] Although the precise molecular mechanisms underlying the progression of NAFLD remains unclear,[34] the accumulation of triglycerides is proposed in the early stages of NAFLD/NASH, whereas insulin resistance, oxidative stress and inflammation are all important contributing factors in disease progression.[35,36] Inflammation is characterised by c-Jun N-terminal kinases activation[34] and reactive oxygen species production derived from the metabolism of excessive free fatty acids *via* microsomal cytochrome P450A oxidation, peroxisomal β-oxidation, and hepatic mitochondrial dysfunction.[37,38]

To date there are two major categories of NAFLD therapies: (i) lifestyle intervention (weight loss, physical exercise) and (ii) pharmaceutical therapies (insulin sensitizers, lipid-lowering agents).[33] Considering insulin resistance plays a core role in the pathogenesis of NASH, glitazones and peroxisome proliferator-activated receptor γ agonists used in the treatment of type 2 diabetes have been comprehensively studied.[39] In particular, Thiazolidinedione (TZD), an insulin sensitizer has been shown to improve hepatic biochemical and histological parameters in patients.[40] Similarly, treatment with the TZD pioglitazone led to a reduction in aspartate aminotransferase (AST) levels by 30-58%, improved hepatic insulin sensitivity, and reversed steatosis in NASH patients.[39] TZDs also reduced the expression of genes linked with inflammation such as interleukin-6 and TNF-α, and possessed regulatory properties through proliferator-activated receptor γ activation of adipokines, the latter possessing crucial roles in the pathogenesis of NAFLD.[41] Furthermore, in diabetic patients with NASH, a phase II double blind trial demonstrated that pioglitazone significantly decreased steatosis, inflammation and ballooning necrosis.[42]

However, there is variable data from TZDs studies regarding regression of fibrosis.[39] A meta-analysis showed that pioglitazone, but not rosiglitazone reduced fibrosis.[43] However, a large trial comparing 'Pioglitazone versus Vitamin E for the treatment of non-diabetic patients with NASH' showed improved

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-106

histology in NASH patients who received pioglitazone but no significant improvement in fibrosis stage for either treatment.[44] Despite the promising results of these pioglitazone studies, the adverse effects of TZD such as weight gain, increased bladder cancer risk and cardiovascular morbidity has limited the use of pioglitazone in patients with NASH.[45] Although vitamin E (400 IU/day) demonstrated some benefit to NASH subjects as shown by reduced inflammation,[44,46] other reports suggest vitamin E is associated with cardiac morbidity including heart failure and haemorrhagic stroke.[47]

Thus targeting insulin resistance and oxidative stress is crucial but not adequate for effectively treating NASH, signifying the need for wider hepato-protective agents. Emerging evidence suggests beneficial properties of bile acids and their derivatives in the treatment of NAFLD by regulating lipid and glucose pathways, reducing inflammation and lowering hepatic triglyceride levels.[3] Agonists have been developed targeting FXR receptors as a therapeutic approach in NAFLD as discussed below.

ROLE OF FXR IN NAFLD

Evidence of the vital role that FXR plays in NAFLD has been observed in FXR null mice. Here FXR null mice present with hepatic steatosis, inflammation, elevated bile acid levels, hyperlipidaemia and fibrosis.[48] Furthermore, in FXR deficient mice fed a 1% cholesterol diet, mice exhibited severe muscle wastage, raised hepatic cholesterol content and a 23-fold greater increase in hepatic triglyceride. Additionally, excessive levels of bile acids correlated to 30% mortality in FXR deficient mice by day 7, which was attributable to liver failure.[49] Gut derived lipopolysaccharide also plays a crucial role in the pathogenesis of NASH.[50] Increased lipopolysaccharide stimulates nuclear factor kappa β which acts to recruit inflammatory cells, thus promoting inflammation, fibrosis and carcinogenesis in advanced NAFLD.[51] In FXR null mice, inflammation was characterised by increased TNF-α and interleukin-1β levels, high circulating and hepatic bile acid levels as well as spontaneous hepatocellular carcinoma at 12 months.[52] Although these studies indicate a causal link between elevated bile acids and inflammation, FXR activation has been shown to suppress the nuclear factor kappa β pathway, as well as the inflammatory cytokines and cyclooxygenase-2 in hepatocytes.[53]

FXR activation also regulates carbohydrate metabolism.[54] Administration of cholic acid to C57BL/6J mice led to a decrease in fasting glucose concentration and reduced expression of the phosphoenolpyruvate carboxykinase gene in the liver, and also in HepG2 cells incubated with chenodeoxycholic acid.[36,55] Other studies found that administration of the FXR agonist GW4064 to streptozotocin-induced diabetic rat or adenovirus-mediated activation of hepatic FXR reduced phosphoenolpyruvate expression and reversed hyperglycaemia and normalised glycogen storage.[55,56] Thus, FXR is thought to regulate gluconeogenesis through its key enzyme phosphoenolpyruvate carboxykinase.[57] These studies suggest activated FXR ameliorates lipid and glucose metabolism and prevents inflammation, thus such properties of FXR make it a novel therapeutic approach in NAFLD treatment.

FXR AGONISTS IN NAFLD AND NASH

A variety of studies have targeted FXR to modulate the metabolism of lipids, carbohydrates and bile acids in NASH,[58] with the synthetic agonist GW4064 widely studied. Here, FXR deficient mice show both systemic and hepatic insulin resistance, which can be normalised by giving the FXR agonist GW4064.[59] In a diabetic mouse model lacking leptin receptors, treatment with GW4064 for 5 days led to a substantial decrease in the plasma levels of glucose and triglycerides.[58] Whereas administration of GW4064 normalised steatosis and serum triglycerides levels in aged mice possibly due to the reduction in endoplasmic reticulum stress.[60] Finally, GW4064 reduced bile acid synthesis, and increased bile acid export in a model of cholestasis.[61] In alternate models of NASH, C57BL/6 mice fed a methionine and choline deficient diet and treated with the FXR agonist WAY-362450 for 4 weeks showed a decline in serum AST and ALT levels, improved liver histology and decreased inflammatory cell infiltration and fibrosis.[29] These studies indicate that FXR agonists may be useful for the treatment of NASH and related liver disorders by normalising carbohydrate, lipid and bile acid metabolism.

Obeticholic acid (OCA) is a synthetic bile acid analogue, also known as INT-747 and the 6α-ethyl derivative of CDCA, and was originally identified in 2002 for its hepatoprotective and anti-cholestatic properties in a model of cholestasis, protecting hepatocytes against acute necrosis triggered by LCA.[62] Interestingly, OCA synthesised through the addition of the ethyl group to CDCA exhibits 100-fold greater agonistic activity than CDCA and this potency has been confirmed by the analysis of the co-crystal structure of the FXR ligand binding domain.[63]

OCA has been studied in a rabbit model of the metabolic syndrome and in the Zucker rat model of obesity where administration of OCA improved glucose and insulin tolerance and decreased steatohepatitis.[64,65] Furthermore, FXR activation by OCA decreased hepatic expression of genes involved in fatty acid synthesis including sterol regulatory element binding protein-1, reduced TNF-α levels and elevated peroxisome- proliferator activated receptor alpha expression, which therefore led to an improvement in the NASH phenotype.[53,65] OCA therapy also reduced inflammation in a FXR deficient model of autoimmune hepatitis and prevented hepatic stellate cell activation by inhibiting osteopontin production.[66,67] In the thioacetamide rat model of fibrosis, OCA prevented fibrosis progression, reversed fibrosis and cirrhosis development, and significantly reduced portal hypertension.[53] Therefore, these preclinical findings have established the anti-inflammatory and anti-fibrotic properties of OCA mediated by FXR, as a candidate agent for NASH/NAFLD treatment.

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-106

FXR AGONISTS IN CLINICAL STUDIES

To date there are only a handful of studies investigating FXR agonists in NAFLD. A small study of patients with type II diabetes and NAFLD showed a marked improvement in insulin sensitivity of 28% when given 25 mg of OCA for a short 6 week period.[68] Furthermore, endogenous levels of bile acid decreased, as well as markers of inflammation and fibrosis.[68] However, the largest clinical trial to date 'Farnesoid X receptor ligand Obeticholic Acid in Non-Alcoholic Steatohepatitis' (FLINT) study has been partially reported in NASH patients receiving oral OCA 25 mg for 72 weeks.[69] Preliminary findings indicated a 45% improvement in liver histology compared to 21% of the placebo group.[69] Similar to the previous study in diabetics, lower levels of ALT in the group were noted as well as an increase in serum alkaline phosphatase, despite decreased gamma-glutamyl transferase levels. Pruritus an adverse effect of OCA treatment was observed in 23% of the OCA group compared with 6% of the placebo group, thus these OCA treated patients may require symptom management.[69] Despite these promising results longer term clinical studies are required to explore the impact of OCA as well as other FXR agonists in the treatment of NASH/NAFLD. There is some evidence indicating that OCA treatment leads to a significant increase (~20%) in LDL-cholesterol levels, which was apparent in the FLINT study,[69] the earlier study on diabetes and NAFLD[66] and in the treatment of diarrhoea.[70] Authors from the FLINT study suggested that this atherosclerosis risk requires careful monitoring and OCA treatment withdrawn in these cases. This clearly may have a negative impact for the long term usage of OCA, despite the clinical benefit on liver histology parameters. One of the original bile acids used clinically for NASH was ursodeoxycholic acid (UCDA). This has been comprehensively reviewed elsewhere,[71,72] but earlier studies did not report an improvement in liver histology or liver enzymes after 2 years of treatment at a low dose of 13-15 mg/kg[73] or 6 months at a high dose of 28-32 mg/kg,[74] but was effective at a high dose after 1 year of treatment.[75] Whilst the long term benefit of UCDA requires confirmation, a taurine conjugate of UCDA called tauroursodeoxycholic acid may have potential use, as this has shown to prevent NASH progression by decreasing endoplasmic reticulum stress.[76]

ALTERNATIVE THERAPIES

Alternative treatment options may offer immediate solutions such as exercise/weight loss programmes, insulin sensitizers[33] or bariatric surgery, which has proven to reduce steatosis, inflammation and moderate amounts of fibrosis in NAFLD patients.[33,77-79] However, like OCA, the long term benefit of bariatric surgery still requires investigation.

CONCLUSION

Novel therapeutic approaches to manage the chronic liver disease epidemic are becoming essential and FXR agonists present as an attractive class of drug for the treatment of NASH/NAFLD. As reviewed, bile acid-activated FXR regulates key homeostatic mechanisms including carbohydrate, lipid, and bile acid metabolism whilst also inhibiting inflammatory and fibrogenic responses. However, the precise mechanisms are still being investigated as well as the impact of intestinal bile acids, on FXR activation. Despite this, pre-clinical and clinical evidence support the notion that therapy with the first-in-class FXR agonist obeticholic acid has the potential to effectively and safely treat chronic liver diseases such as NAFLD.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

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ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-107

Mini Review

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Volume 1 : Issue 2
Article Ref. #: 1000LROJ1107

Article History:
Received: July 10th, 2015
Accepted: July 27th, 2015
Published: July 29th, 2015

Citation:
de Siqueira ERF, Pereira LMMB, Sanyal AJ. Cardiovascular disease and NASH. *Liver Res Open J*. 2015; 1(2): 41-44.

Cardiovascular Disease and NASH

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) and Non-alcoholic steatohepatitis (NASH) are associated with cardiovascular events and Metabolic Syndrome (MetS). NAFLD is considered to be a hepatic manifestation of MetS and has become an important public health issue because of its high prevalence. It is currently being considered an independent Cardiovascular disease (CVD) risk factor. In this clinical review, we will briefly review the mechanisms linking NAFLD to the complement system, endothelial dysfunction and the atherosclerosis.

KEYWORDS AND ABBREVIATIONS: NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; CVD: Cardiovascular disease; MetS: Metabolic Syndrome: AF: Atrial Fibrillation; CAC: Coronary Artery Calcium; CT: Computed Tomography; FFAs: Free Fatty Acids; LDL-C: Low-density Lipoprotein-Cholesterol; HMGCR: HMG CoA Reductase; VLDL: Very-low-density lipoprotein; CAD: Coronary Artery Disease.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become a predominant cause of chronic liver disease in many countries. Excess body weight predisposes individuals to chronic diseases such as cardiovascular disease (CVD), Type 2 Diabetes Mellitus (T2DM) and NAFLD. NAFLD and cardiovascular disease is obesity related MetS and it is increasing virtually in all age groups worldwide.[1] Approximately 10-30% have the potentially progressive form of NAFLD to Non-alcoholic steatohepatitis (NASH), which is associated with hepatocellular injury, inflammation and ultimately resulting in cirrhosis in 20-30%.[2-4]

A population-based study of 980 NAFLD patients and 6,594 controls followed long term (mean: 8.7 years) showed that NAFLD patients had significantly increased all-cause mortality and cardiovascular mortality, especially in the 45-54 years age group.[5] Another study that linked NHANES III participants to follow-up mortality data showed that cardiovascular disease was the leading cause of death in patients with NAFLD.[6]

Several evidences support the association of NAFLD/NASH and the occurrence of cardiovascular events, such as increased carotid intima-media thickness, increased coronary artery calcification, impaired flow-mediated vasodilatation and arterial stiffness independent of traditional risk factors and MetS.[7-9]

The finding that NAFLD is associated with an increased risk of Atrial Fibrillation (AF) in people without evidence of co-existing valvular heart disease supports the assertion that NAFLD may also be an emerging risk factor for cardiac arrhythmias.[10,11] Another marker of early coronary atherosclerosis is association of NAFLD and increased Coronary Artery Calcium (CAC) score on cardiac Computed Tomography (CT).[12]

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-107

In this clinical review, we will briefly review the mechanisms linking NAFLD to the risk of cardiovascular events.

MECHANISMS LINKING NAFLD WITH CARDIOVASCULAR EVENTS

Data in the literature are still controversial regarding the increased cardiovascular risk with NASH. A large North American database reported a higher prevalence of CVD risk factors and events in patient with NAFLD in comparison with those without. Nonetheless, the rate of CVD mortality was not high in subjects with NAFLD.[13] Previous studies have already demonstrated the presence of NAFLD independently increased the risk for Coronary Artery Disease (CAD) and NAFLD was more commonly found in patients as the extent of CAD increased (P=0.001).[14] It has also been shown that risk, after adjustment for age, sex, race, ethnicity, body mass index, and hyperinsulinemia, children with MetS had 5.0 times the odds of having NAFLD as overweight and obese children without MetS.[15]

In another prospective, Japanese study of 1221 apparently healthy subjects, patients with NAFLD showed an increased incidence of CVD events (1.0% *vs.* 5.2%; P<0.001) and NAFLD emerged as an independent predictor of CVD.[16] However, there were no differences in the incidence of fatal CVD, non-fatal myocardial infarction, and coronary revascularization after the follow up.[17]

The CVD is characterized by critically narrowing (stenosis) or occlusion (atherothrombosis) of blood vessels. Key processes in CVD are endothelial dysfunction, atherosclerosis, and impaired regulation of coagulation and fibrinolysis. The complement system may be involved in all these processes based on its immune, inflammatory and metabolic functions.[18]

Furthermore, systemic complement levels may be involved in coagulation and fibrinolysis, which together with endothelial dysfunction and atherosclerosis result in cardiovascular disease.[18] The complement-C3 has shown independent associations with insulin resistance, liver dysfunction and in the risk of MetS and T2DM.[19,20]

Circulating levels of several inflammatory markers (C-reactive protein, interleukin-6, monocyte chemotactic protein 1, and TNF-a), procoagulant factors (plasminogen activator inhibitor 1, fibrinogen, and factor VII), and oxidative stress markers are highest in patients with NASH independent of obesity and other potentially confounding factors.[21] NAFLD seems to be not simply a marker of cardiac and arrhythmogenic complications but also may play a part in their pathogenesis possibly *via* atherogenic dyslipidemia and the hepatic secretion of several pathogenic mediators.[22,23]

Central obesity can provoke inflammation and insulin resistance in adipose tissue and the release of proinflammatory adipokines and Free Fatty Acids (FFAs). Relation of hepatic steatosis to atherogenic dyslipidemia results from previous studies that liver fat is associated with an increased number of higher Low-density Lipoprotein-Cholesterol (LDL-C), in special the small dense LDL (sdLDL) particles, which have higher atherogenic properties than larger less dense LDL-C particles.[24-26]

These lipoproteins are associated with increased activity of hepatic lipase favoring the production of sdLDL particles.[27] Patients with NASH can have the transcriptional regulation of proatherogenic genes altered and it is associated with the activation of molecular events that may also be responsible for the local production of mediators or modifiers of circulatory homeostasis.[28]

In particular, NASH presents a distinct panel of regulatory genes which are dysregulated compared to the control and subjects with simple steatosis. Increased activation of genes involved in cholesterol biosynthesis and metabolism by Sterol Regulatory Element-binding Protein-2 (SREBP-2), the principal transcriptional activator of the HMG CoA Reductase (HMGCR), the metabolic pathway that produces cholesterol and other isoprenoids, is a key factor driving both the LDL-C and accumulation of hepatic free cholesterol.[29,30]

NAFLD is associated with increased Very-low-density lipoprotein (VLDL) particle concentration and apolipoprotein b (ApoB), sdLDL particle concentration and cholesterol content. The triglyceride levels, VLDL particle concentration and size as well as ApoB were directly related to the degree of fasting insulin levels which is consistent with the known effects of insulin on triglyceride synthesis.[31]

The atherogenecity of the increase in sdLDL is likely to be further compounded by our previously noted decrease in LDL receptor expression in NASH.[29] From a cardiovascular point of view the direct relation between LDL-C and HMGCR expression suggests that the liver disease contributes to LDL-mediated cardiovascular risk.[29]

CONCLUSION

In this context, the liver represents also a contributor to systemic inflammatory changes, insulin resistance and hyperlipidemia determining a progression of vascular diseases and atherosclerosis. NAFLD/NASH are associated with an increased risk of incident cardiovascular disease, independently of the traditional risk factors. Therefore, a multidisciplinary approach to patients with multiple risk factors including MetS and T2DM is required to monitor for cardiovascular and liver complications.

DECLARATION OF INTEREST

The authors declare that they have no competing interests.

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ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-108

Case Report

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Volume 1 : Issue 2
Article Ref. #: 1000LROJ1108

Article History:
Received: August 5th, 2015
Accepted: August 12th, 2015
Published: August 12th, 2015

Citation:
Liao H, Yan Z, Peng W, Hong H. Hepatic myelopathy: case report and review of the literature. *Liver Res Open J*. 2015; 1(2): 45-55.

Hepatic Myelopathy: Case Report and Review of the Literature

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ABSTRACT

Background: Hepatic Myelopathy (HM) is a rare complication of chronic liver disease usually associated with extensive portosystemic shunt of blood, which has been created surgically or has occurred spontaneously, causing progressive spastic paraparesis. Some single cases or short clinical reports describing patients suffering from HM have been published worldwide, but are often scattered.
Material and method: One additional case of HM with typical symptoms was presented, and a retrospective survey of the literature in a manner of comprehensive review was undertaken.
Results: 46 case reports with 98 patients of HM including ours have been eligibly selected. General information on all cases was summarized. Detailed analysis of the clinical characteristics of HM patients was undertaken.
Conclusion: Liver cirrhosis caused by hepatitis B infection and alcoholism is the most frequent causes of HM. Portosystemic shunt which resulted in chronic exposure to toxic substances bypassing the liver play an important role in the pathogenesis. The pathology study consistently disclosed a selective and symmetrical severe loss of myelin in both lateral pyramidal tracts. The predominant neurologic abnormality of HM is the progressive spasticity and weakness in the lower extremities. A typical manifestations, such as triparesis or quadriparesis, sensory deficit, urinary or bladder incontinence and non-pyramidal manifestations such as dysarthria, tremor and ataxia can also occur, which render the disorder more complicated to be diagnosed. Plasma ammonia concentrations were frequently found to be elevated. MEP provides evidence of the early diagnosis of HM and assesses different degrees of neurological involvement. The spinal cord MRI imaging shows no abnormality. Abnormalities of brain magnetic resonance combined with syndrome of brain dysfunction, hepatocerebral degeneration should be taken into consideration. Appending case studies suggest that liver transplantation is a promising therapeutic strategy.

KEYWORDS: Hepatic myelopathy; Spastic paraparesis.

ABBREVIATIONS: HM: Hepatic Myelopathy; CLD: Chronic Liver Disease; HE: Hepatic Encephalopathy; AHCD: Acquired hepatocerebral degeneration; HTLV-1: Human T-cell Lymphotrophic Virus; MRI: Magnetic Resonance Imaging; TIPS: Transjugular Intrahepatic Portosystemic Shunt; HIV: Human Immunodeficiency Virus; OLT: Orthotopic Liver Transplantation.

INTRODUCTION

Patients with Chronic Liver Disease (CLD) frequently experience neurologic sequel, usually associated with extensive portosystemic shunt of blood, a liver bypass either by portosystemic anastomosis or as a result of the development of an extensive portosystemic collateral

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-108

circulation. The most common and widely recognized is the reversible syndrome of Hepatic Encephalopathy (HE). There are also comparatively rare and largely irreversible conditions such as Acquired hepatocerebral degeneration (AHCD)[1] and hepatic myelopathy (HM),[2] especially the knowledge on HM is sparse. The predominant neurologic abnormality of HM is the progressive spasticity and weakness in the lower extremities which often render the patient to become wheelchair bound. Since Leigh and Card, firstly described the occurrence of HM in 1949, some single cases or short clinical reports describing patients suffering from HM have been published worldwide,[3] but are often scattered. Herein the author presented one additional case of HM with typical symptoms and undertook a retrospective survey in a manner of comprehensive review in order to determine the clinical and pathophysiological features and treatment of HM.

CASE REPORT

A 29-year-old man was admitted on November 25, 2009, because of a progressive spastic paraparesis which had proceeded over the previous 2 months. The patient complained for the first time of symptoms of stiffness and weakness of legs. Gradually his walking became unsteady, tripping over objects. On admission, he could stand without support but was not able to walk without help. He walked leaning forward with his feet close together, with 'step page' or puppet-like gait. He was suffering from posthepatitic cirrhosis caused by hepatitis B with a history of 6 years, having ascites as the initial presentation in 2003, but constantly without prior recurrent episodes of hepatic encephalopathy. Four years back, he had recurrent jaundice and pedal edema but no hematemesis. In 2008, he received blood transfusion because of thrombocytopenia. He had neither history of alcohol consumption nor family history of liver or neurological illness. On examination, the patient was alert, cooperative and orientated. He had no speech disturbance. He had palmar erythema, spider-angioma, and peripheral edema. The abdomen showed small venous collaterals and marked generalized distension with fluid wave due to ascites. The enlarge spleen was palpable three finger-breadths below the costal margin, firm and nontender. Liver and kidney was not palpable. There were no Kayser-Fleischer corneal rings. On neurological examination, cranial nerve examinations were normal. Spastic paraparesis was observed. Muscle tone was markedly increased, particularly in the lower limbs, with pathologically brisk deep tendon reflexes and bilateral extensor plantar responses, and there was clonus at the ankles, but no sensory loss. Muscle strength in the lower limbs was decreased (MRC grade 4). There was neither atrophy nor fasciculation. Bowel and bladder function were normal. There was no evidence of cerebellar or extrapyramidal dysfunction. Laboratory findings revealed increased plasma bilirubin and ammonia levels. Prothrombin time was prolonged. Hemogram disclosed thrombocytopenia, leucocytopenia and normocytic hypochromic anemia. Liver function tests revealed normal serum bilirubin, minimally raised alanine aminotransferase and aspartate aminotransferase, reduced albumin, and reversed albumin/globulin ratio. Serum Vitamin B12 and foliate values were within normal ranges. Serum antibodies to Human T cell lymphotrophic virus (HTLV-1) and Hepatitis C virus were absent. Anti-HBs was negative, and HBsAg, anti-HBc, anti-HBe positive. Copper values of serum and urine were normal. Small esophageal and gastric varices were demonstrated during the upper gastrointestinal endoscopy. Lumbar puncture could not be performed because of his severely impaired coagulation status. Ultrasound (abdomen) exhibited features of cirrhosis of liver: irregular liver surface and different echogenicity in the underlying liver. Doppler study showed functioning lienorenal shunt, recanalized umbilical venous and extensive collateralization. EEG was normal. Cranial Magnetic Resonance Imaging (MRI) showed no abnormalities. MRI of the whole spinal cord was normal except degenerative bone changes in the area of L4-5, L5-S1 without evidence of spinal cord compression. The electromyographic evaluation for second motor neuron involvement was also normal. It was suggested that the features in our patient were typical of HM: spastic paraplegia occurred during the course of liver cirrhosis, which is progressive and permanent. After several weeks of lactulose administered by rectum, neomycin, protein restriction, combined with oral lioresal, he had improved mobility, with decreased spasticity but no significant changes in the remainder of his neurological examination and was discharged one month later.

REVIEW OF LITERATURE

A computerized search of the US National Library of Medicine database of literature (Pubmed), ISI Web of Knowledge databases and cross-referencing was conducted. Broad key word phrases, including "hepatic", "liver", "cirrhosis", "postshunt", "portacaval", "portosystemic", "portal-systemic" were used in conjunction with the terms, including "myelopathy", "spinal", "paraplegia". English language articles published are included. To identify further published and unpublished, reference lists of relevant articles were searched. Abstracts were reviewed and articles unrelated to the specific topic were excluded. Duplicate references and redundant publications were discarded by the first author.

The patients were classified into 4 classes with the Expanded Disability Status Scale (EDSS) disability scale[4] according to the severity of the motor dysfunction. Patients who did not complain of neurological symptoms nor did objective examination reveal any were grade 0; Patients who had mild neurological abnormalities (hyperreflexia, extensor plantar responses) without disability were grade 1; Patients who experienced minimal disability (stiffness, nocturnal spasms and leg cramps) were grade 2; Patients who had neurological abnormalities (mild or moderate paraparesis) were grade 3.

RESULTS

46 case reports with 98 patients of HM including ours

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-108

have been eligibly selected. General information on all cases was recorded (see supplement Materials Table 1, Table 2). Detailed analysis of the clinical characteristics of HM patients was undertaken.

89 cases had detailed information in the Etiology. The underlying Etiology of HM was as follows (summarized Table 1): 74(83.1%) liver cirrhosis including 34(38.2%) posthepatitic cirrhosis, 21(23.6%) alcoholic cirrhosis, 3(3.4%) biliary cirrhosis, 16(18.0%) cryptogenic cirrhosis, and 15(17%) cryptogenic cirrhosis, the remaining 15(16.9%) non-Liver cirrhosis diseases including 8(9.0%) longstanding alcoholism without cirrhosis, 3(3.4%) idiopathic portal hypertension,[5] 1(1.1%) chronic active hepatitis, 2(2.2%) congenital hepatic fibrosis,[6,7] and 1(1.1%) adult-onset type II citrullinemia.[8]

Among the 93 patients who had detailed information about the history of portosystemic shunting, 57(61.3%) had taken different types of shunting surgery, including portocaval shunt (25/57, 43.9%), splenorenal shunt (11/57, 19.3%) and transjugular intrahepatic portosystemic shunt (8/57, 14.0%). Besides this, 16(18.3%) cases were demonstrated to have spontaneously occurred portosystemic collateral circulation with no history of surgical shunting. However, there were still 20 cases (21.5%) with either surgical or idiopathic shunting.

Characteristic	
Etiology (n=89)	
Liver cirrhosis	74(83.1%)
Posthepatitic cirrhosis	34(38.2%)
Alcoholic cirrhosis	21(23.6%)
Biliary cirrhosis	3(3.4%)
Cryptogenic cirrhosis	16(18.0%)
non- Liver cirrhosis	15(16.9%)
Alcoholism without cirrhosis	8(9.0%)
Idiopathic portal hypertension	3(3.4%)
Chronic active hepatitis	1(1.1%)
Congenital hepatic fibrosis	2(2.2%)
Adult-onset type II citrullinemia	1(1.1%)
Portosystemic shunt	
Created surgically	57(58.2%)
Portacaval shunt	25/57(43.9%)
Splenorenal shunt	11/57(19.3%)
TIPS	8/57(14.0%)
Unknown	13/57(22.8%)
Occurred spontaneously	16(18.3%)
No	20 (21.5%)
Unknown	5

Table1: Etiology of HM.

We are able to retrieve 8 articles with 9 cases of postmortem pathological studies which described the histological changes of HM in detail (summarized in Table 2). In the spinal cord, a selective and symmetrical severe loss of myelin was noted in both lateral pyramidal tracts in all cases, sometimes (4/9) associated with various degree of axonal loss.[9,10] Such finding first becomes noticeably evident in the low cervical cord and becomes more intense at lower levels.[11,12] The degeneration of lateral columns does not extend beyond the upper cervical cord.[8] In a majority of the cases (7/9) secondary reactive changes due to demyelination with significant numbers of macrophages with an abundance of intracytoplasmic sudanophilic materials (so-called lipid-laden macrophages)[12] were found,[13] but only in 2 cases (2/9) rare perivascular lymphocytic infiltration was present.[10,13] Occasionally, Minor demyelination had also been found in the ventral pyramidal tracts (2/9), the posterior columns (5/9),[9,10] the spinothalamic tracts or spinocerebellar tracts (2/9).[12] There was no loss of myelin within the dorsal roots at any level of the spinal cord, and the gray matter was relatively intact.[10] Histological examination of the arterial and venous spinal vessels revealed normal findings.[12]

Characteristic	
Cerebral changes	8/9
Betz cell count decreased	2/9
Cerebrum	8/9
Globus pallidus	5/9
Putamen	5/9
Spinal cord changes	9/9
Demyelination	9/9
the lateral pyramidal tracts	9/9
the ventral pyramidal tracts	2/9
the posterior columns	5/9
the spinocerebellar tracts	2/9
Axonal loss	4/9
Secondary reactive changes	7/9
Perivascular round cell infiltration	2/9

Table 2: Pathological features of HM (n=9).

In the brain, cortical structures were normal. In the motor cortex the number of Betz cells was decreased in only 2 cases.[10,12,14] The pyramidal tracts were noted to be normal as they pass through the internal capsules and brainstem.[8,15] Significant numbers of protoplasmic astrocytes, the so-called Alzheimer type II astrocytes and spongy degeneration[3] were found in the cerebrum (8/9), globus pallidus (5/9) and putamen (5/9), which was a histologic feature of HE. When combined with AHCD, the neuropathologic findings included diffuse but patchy cortical necrosis, and uneven neuronal loss in the cerebral cortex, basal ganglia, and cerebellum.[10,14,16,17]

Clinical features were summarized in Table 3. The patients ranged in age from 14-76 years with the mean age of 45. The sex ratio (male/female) was 6.3/1(82/13), male was strikingly predominant in HM. The interval between shunt surgery and onset of neurological illness varied from 1 month to 33 years, with a median of 24 months (n=49). According to the de-

tailed history in 71 patients, a majority of 50 cases (70.4%) had a history of relapsing HE. Among them, 41(82.0%) cases suffered from paraparesis with HE or after several episodes of HE, but in 6(12.0%) patients, HM was precede HE. 21(21.4%) developed HM onset without any episodes of encephalopathy.

Characteristic	
Demography	
Mean age (years±SD) (n=98)	45±13
Sex (n=95)	
Male	82(86.3%)
Female	13(13.7%)
Hepatic encephalopathy	
Yes	50(51.0%)
Before HM	41/50(82.0%)
After HM	6/50 (12.0%)
UK	3/50 (6.0%)
No	21(21.4%)
UK	27(27.6%)
Shunt history (median, n=49)	24 months
Progression Time (median, n=46)	6 months
Clinical manifestation	21(23.6%)
Involvement of the upper limbs (n=84)	11/84(13.1%)
Superficial sensation deficit (n=73)	6/73(8.2%)
Deep sensation deficit (n=75)	14/75(18.7%)
Sphincter incontinence (n=74)	8/74(10.9%)
non-pyramidal manifestation (n=81)	21/81(25.9%)
EDSS disability scale (n=46)	
grade 1	9/46(19.6%)
grade 2	20/46(43.5%)
grade 3	17/46(37.0%)
Blood ammonia elevated (n=67)	54/67(80.6%)
Brain MRI abnormality (n=45)	21/45(46.7%)

Table 3: Clinical features (n=98).

The clinical manifestations of hepatic myelopathy are gait difficulty with insidious onset and progressive course varying from 1 months to 7 years (median 6 months, n=46) finally reaching a relatively stable condition. After months, the process plateaus, leaving most patients relatively stable with different conditions of patterns, either mild neurological abnormalities (hyperreflexia, extensor plantar responses) without disability (9/46, 9.6%) or minimal disability (stiffness, nocturnal spasms and leg cramps, dependent upon an assistive device) (20/46, 43.5%) or neurological abnormalities (mild or moderate paraparesis, confined to a wheelchair) (17/46, 37.0%).

The upper extremities affection is affected minimally and not common but there are still 11 cases (13.1%) well documented.[15,18] In addition to spastic paraparesis or quadriparesis, 6 cases (8.2%) manifested superficial sensation deficit,[2,3,18-22] 14 cases (18.7%) had deep sensation deficit and 8 cases (10.9%) had sphincter incontinence.[3,16,18,23] Non-pyramidal manifestation such as dysarthria, tremor and ataxia was observed in 21 cases (25.9%).

In a majority of the cases (54/67, 80.6%), plasma ammonia concentrations were found to be elevated. The spinal cord MRI imaging shows no abnormality. MRI of the brain showed high signal intensity on T1-weighted sequences within the basal ganglia including pallidum, lentiform nucleus, putamen, internal capsule and extensive white matter disease on T2-weighted sequences[7,18] in 21 cases (46.7%).

To date, there were only 15 cases undergone OLT in the English literature, altogether 11 cases showed quite impressive improvement,[18,21,24-26] mostly recovered to be ambulatory.

DISCUSSION

Etiology

HM has been associated with a broad range of liver diseases, especially those involving portosystemic shunt. Since patients with HM now have prolonged survival due to technological advances including liver transplantation, greater understanding and recognition of this rare cause of morbidity will become even more important.

Liver cirrhosis due to hepatitis B and alcoholism are the most frequent causes of HM. The majority of the patients manifested typical symptoms in the end stage of liver disease with prior evidence of liver dysfunction such as hepatic encephalopathy, upper gastrointestinal tract hemorrhage, ascites or otherwise a history of portosystemic shunt. However, 15 cases without cirrhosis have been reported including longstanding alcoholism and chronic active hepatitis. It seems that cirrhosis is not the only form of liver dysfunction which results in the chronic toxic substances bypassing the liver that causes both HM.

Pathophysiology

At present, the pathophysiology of HM remains poorly understood. In 1960, Zieve[16] pathologically described HM as a symmetric loss of myelin in the lateral corticospinal tracts; this may have led to the finding that HM is characterized by motor involvement of the lower limbs without clinical sensory abnormalities.

The fact that HM occurred most often in cirrhosis patients accompanied by HE onset suggested that HM might involve mechanisms similar to HE. Portocaval shunts, or less commonly splenorenal shunts appear to have a substantive role in the neurologic deterioration.[20] The common belief is that the nitrogenous breakdown products or a neurotoxin by-passing the liver through the portocaval shunts even in the absence of liver dysfunction.[6,8] Demirci, et al.[6] reported a case with total

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-108

portosystemic shunt, which developed spontaneously due to congenital hepatic fibrosis. Cellular functions of the liver, except for an elevated blood ammonia level, were within normal limits, as is usual in congenital hepatic fibrosis. This case showed that spastic paraparesis following portosystemic shunt may occur without liver failure. The structure alteration occurs only after a fairly long-term exposure to ammonia and other putative neurotoxins shunt around the liver. Shunt is the key event for the long-term process in the pathogenesis of this disorder. The portocaval shunts can occur either spontaneously, after surgery, or due to 'functional shunting' – filtration of portal blood through a non-functioning liver. However, there were still 20 cases (21.5%) without either surgical or idiopathic shunting. This may be due to the difficulty in finding some hiding collateral circulation such as the retroperitoneal varices.[18] Patients with AHD or HM should initially be evaluated for the presence of portosystemic shunts.

Given the apparent relationship to shunt, it would seem most likely that it is chronic exposure to toxic substances bypassing the liver that causes both AHCD and HM, with different pathologic response in the brain or spinal cord.[7] Ammonia is the most frequently implicated agent. In Tazawa's case,[8] the patient diagnosed as adult-onset type II citrullinemia (CTLN2) which is characterized by highly elevated levels of citrulline and ammonia in the plasma, is unique in developing hepatic myelopathy without portocaval shunt. Delivery of nitrogen containing substances into the systemic circulation results in nervous system intoxication. Otherwise, Sage, et al.[27] and Imai, et al.[28] respectively reported 5 and 1 alcoholic cases without substantial liver disease. The absence of portacaval shunt or notable liver dysfunction in these patients suggests that a direct toxic effect of alcohol must be considered a possible mechanism of spinal cord damage. Other candidate substances such as high manganese or mercaptan levels may play a role in etiopathogenesis of HM. Although the cerebral deposition of manganese may have a role in the etiopathogenesis of AHD, there was no report in HM.[18] Though various hypotheses were suggested, the above seems to gain agreement consistently. However, the possibility of a deficiency of a needed liver-synthesized material cannot be excluded.

Regarding the topography of the spinal cord lesions in HM, it has been suggested that HM might be related to hemodynamic factors because the lesions observed are located just within those spinal segments that miss an extensive collateral circulation,[13,29] this was once assisted by Giangaspero's case that degeneration of the lateral corticospinal tracts was associated with diffuse bilateral ischemic changes of the spinal gray matter in absence of any anatomical cause of spinal cord infarction, although to date no other support this contention. HM might also be caused by nutritional factors because similar pathologic changes have been described in the spinal cord of prisoners of war and patients suffering from malnutrition.[3,29,30]

Some investigators have raised the question of whether spinal cord damage is direct or only a secondary effect of damage to cerebral cortical Betz cells. Pant, et al.[9] noted a decrease in the number of Betz cells in the cerebral cortex in their two cases, and discussed the more distal demyelination at the lateral column as a "dying back" phenomenon from the peripheral to the neuron. In the vast majority of reported cases, episodes of overt hepatic encephalopathy preceded the appearance of myelopathy, and thus it is likely that this corticospinal tract lesion simply represents the damage accumulated from multiple episodes of hepatic encephalopathy.[31]

The author also noted the selectivity of the disease to the corticospinal tracts, sparing other system in the cord, and suggested damage to the cerebral cells of origin; it is more likely a restricted encephalopathy rather than a myelopathy. However, more cases with a normal number of Betz cells and spinal cord demyelination and gliosis involving, but not limited to, the corticospinal tracts, have been reported subsequent to the report of Pant, et al.[9] In addition, as pointed out by Lefer, et al.[10] the rather abrupt cessation of demyelination at the cervical segment in almost all cases despite greatly varying durations of the disease is not the case expected for a progressive dying back process. It seems that either the pathogenic mechanism affects the corticospinal tracts directly at the spinal cord, or less likely, some other factors limit the dying back below the cervical level.[6]

Thus, while portosystemic shunting may precipitate both HM and AHCD, it probably does so by diverse mechanism. The fact that HM and AHCD differ pathologically is consistent with this supposition.[32] A discrepancy exists between the tissue reaction in the corticospinal tract and sparing of other systems in the spinal cord, where axonal degeneration and demyelination, cytoplasmic astrocytosis and round cell infiltration occur, and the reaction in the brain and brain stem, where there is proliferation of Alzheimer type II glial cells. This discrepancy of the sensitivities indicates that there are two pathogenic mechanisms, one responsible for the lesions in the brain and brain stem and the other for those in the spinal cord. Alternatively, a single factor may be responsible for the development of both lesions, and morphologic discrepancy reflects differences in the sensitivity of the tissues in these two general areas.[10]

Clinical Features

The intervals between the construction of a shunt and the diagnosis of portosystemic myelopathy were shorter in Transjugular Intrahepatic Portosystemic Shunt (TIPS) than in portacaval shunts or splenorenal shunt respectively (see Table 4). This suggests that not only the shunt itself but also the shunted volume contributes to the development of the syndrome, which was approved by Conn, et al.[2] However, it was not agreeable that the difference was not significant between the portacaval shunts and the splenorenal shunt.

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-108

	Portacaval shunt	Splenorenal shunt	TIPS
n	23	9	8
Median interval (months)	24.0	34.0▲	6.5*,*

p<0.05, comparison of portacaval shunt, splenorenal shunt and TIPS using K independent nonparametric Kruskal-Wallis Test.
*p<0.01, comparison of portacaval shunt and TIPS using 2 independent nonparametric Mann-Whitney Test.
*p<0.01,comparison of splenorenal shunt and TIPS using 2 independent nonparametric Mann-Whitney Test.
▲No significance, comparison of portacaval shunt and splenorenal shunt using 2 independent nonparametric Mann-Whitney Test.

Table 4: Intervals between the time of shunt construction and onset of portosystemic myelopathy.

No relation between episodes of HE and presentation or exacerbation of HM was evident. Patients can develop HM at a time when their HE was well controlled.[32]

It can be ignored because walking difficulty can be all too easy to attribute this to a multitude of other problems commonly seen in this group of patients, including peripheral edema, malnutrition, and electrolyte disturbances.[24] Most commonly, symptoms will develop after several bouts of HE, although rarely myelopathy may be the presenting manifestation of liver failure. The signs of corticospinal tract damage appear to accumulate with each episode, although other neurologic signs resolve completely. Initially, the symptoms may be slightly asymmetric, but will invariably affect both legs and steadily worsen. Increased muscle tone and hyperreflexia are the most prominent findings only except one case which might be explained peripheral neuropathy due to HCV infection.[33,34] Almost in all cases, the tendon reflexes were exaggerated in the legs. Various plantar responses including Flexor responses have been described,[19,23,30,35] even in patients with ankle and knee clonus.

In most cases, lower extremities weakness is permanent, but Campellone, et al.[20] reported one case with full recovery over the following 6 months and was fully independent and ambulatory before the onset of his once more neurologic complaints. Reason for this may be explained by the description reported by Conn that his patient's improvement was attributed to decreased portosystemic shunt through the liver, resulting from the occlusion of the TIPS shunt.

Decreased appreciation of pin-prick and vibratory stimulation may be the result of mild peripheral neuropathy and affection of the posterior column degeneration[27,28] mostly in the alcoholic patients. Imai, et al.[28] describe a patient with alcoholic myelopathy presenting sudden electric-like sensations on flexion of the neck, which spread down the body, to the back, or to the extremities, so-called "Lhermitte's sign" as an initial symptom consistent with the MRI finding of posterior column degeneration.

Since HM may be accompanied by the AHCD, if the patient manifests neuropsychiatric (apathy, lethargy, excessive somnolence, secondary dementia, etc) and/or extra pyramidal (focal dystonia, postural tremor, myoclonus, rigidity, dysarthria, choreoathetosis, etc) symptoms, AHCD should be taken into consideration.[7]

Laboratory Findings

There were no significant findings with EEG except a basic rhythm in the theta and occasionally in the delta range, without epileptiform discharge, no phase reversal and no voltage suppression. Lumbar puncture usually reveals no abnormalities other than an elevated glutamine level,[14,35] although increased protein content is rarely noted.[12] Thyroid functions, serum Vitamin B12 and folate values were in normal ranges. Serum antibodies to human T cell lymphotrophic virus (HTLV-1), Human Immunodeficiency Virus (HIV), antinuclear antibodies, syphilis serology were absent. Copper values of serum and urine were normal. Small esophageal and gastric varices might be demonstrated during the upper gastrointestinal endoscopy.

Radiographic Characteristics

Negative spinal cord MRI results supported HM in the differential diagnosis, because MRI was essential to rule out such etiologies involving infarction, myelitis or compression of the spinal cord (epidural cord compression or intrinsic cord tumor). MRI of the brain showed high signal intensity on T1-weighted sequences within the basal ganglia including pallidum, lentiform nucleus, putamen, internal capsule and extensive white matter disease on T2-weighted sequences.[7,18] The toxic effect of the portal blood is greatest in the basal ganglia, probably because of high metabolic activity in this area. The distribution of lesions of this area with greater vulnerability seems to be influenced by blood-derived substances. Such abnormalities were consistent with the non-pyramidal manifestation (see Table 5). The common neuropathological finding in hepatic encephalopathy is the presence of Alzheimer type II glia diffusely with spongy degeneration scattered throughout the cerebral hemispheres including the cerebral cortex, basal ganglia and cerebellum[10] while the spinal cord is intact. In contrast, the reported features of hepatic myelopathy were pyramidal tract lesions located predominantly in the spinal cord, especially in the thoracic cord, with no involvement of the brain stem.[12] We suggest that abnormalities of brain magnetic resonance combined with syndrome of brain dysfunction, AHCD should be taken into consideration.[7] When the posterior column of the cord if affected, MR imaging may reveal abnormal signal intensity in the posterior column spanning the whole length of the upper cervical cord, which is consistent with Lhermitte's sign.[28]

		Brain MRI finding		Total
		+	-	
non-Pyramidal Manifestation	+	10	1	11
	-	11	23	34
Total		21	24	45

p=0.001<0.01, using Pearson Chi-Square.

Table 5: The consistence between Brain MRI finding and non-pyramidal manifestation.

ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-108

Motor Evoked Potentials (MEPs)

Clinical detection of spinal cord dysfunction is difficult in the early stage of the disease. Spinal cord involvement was evident even at the preclinical stage and became more overt as the disease progressed. Transcranial Magnetic Stimulation (TMS) is a reliable method for testing the integrity of the motor pathways and of locating the sites of disruption. MEP studies elicited by TMS which is non invasive may disclose an impairment of the corticospinal pathways even before HM is clinically manifest and provide evidence that early diagnosis of HM. Abnormality of Central Motor Conduction Time (CMCT) for lower limb muscles associated with a normal CMCT for muscles supplied by upper cervical segments suggesting a lesion below the cervical outflow in the spinal cord causing the motor conduction delay.

Otherwise, Clinical conditions and MEP patterns of abnormality were significantly correlated.[36] MEP in assessing different degrees of neurological involvement could be relevant for therapeutic purposes, and in monitoring the progression of the disease. The clinical and neurophysiological features of patients with slight MEP abnormalities improved after OLT, whereas the patients with a more advanced stage of disease (severe MEPs abnormalities) did not, indicating that subsequent immediate liver transplantation have to be recommended.[37]

Differential diagnose

There is no special diagnostic tool for HM. The diagnosis of HM has to be established presumptively on clinical grounds after exclusion of other possible causes of spastic paraparesis, such as demyelination myelopathy, amyotrophic lateral sclerosis, hereditary spastic paraplegia, subacute combined degeneration, Wilson syndrome, cerebral vascular disease, and HIV/human T cell lymphoma virus 1 (HTLV-1) infection.

HM must also be differentiated from other neurological complications of liver disease. AHCD is a permanent, progressive degeneration of the nervous system, causing cognitive, cerebellar, pyramidal, and extrapyramidal dysfunction in various combinations. The typical clinical features are dementia, dysarthria, ataxia, intention tremor, and choreoathetosis. Patients may also exhibit transient upper motor neuron signs.[38] One must be noted that the imaging abnormalities of brain and evidence of spinal cord involvement from cortical magnetic stimulation, in the setting of the clinical findings of significant non-pyramidal neurological signs such as dysarthria, tremor, ataxia, and paraparesis without sensory involvement, suggest that the patient may have both AHCD and HM.

Some degree of pyramidal symptoms is typically seen in the even uncomplicated cases of HE with mild hepatic failure, probably associated with ammonia levels, making it difficult to distinguish early or mild cases of HM, which usually start following an attack of encephalopathy. Usually, non-pyramidal neurologic abnormalities in HE – dysarthria, ataxia, tremor, rigidity, and disturbances of consciousness – are reversible with established treatment for HE. In contrast, spastic paraparesis caused by HM has been shown to be refractory with HE treatment, which aims at lowering plasma ammonia concentrations. This may be explained best as reversible, short-term toxic effects of ammonia on the neuron function, not on neuron structure. Such case would be more appropriate to be considered as a form of hepatic encephalopathy complicated by some symptoms of myelopathy.[39] In contrast, spastic paraparesis caused by HM has been shown to be refractory with HE treatment, which aims at lowering plasma ammonia concentrations.

Treatment

Treatment strategies for HM include liver protection, neurotrophic drugs, measures to control blood ammonia concentration, and liver transplantation. Unlike HE, the conservative treatment of HM is usually considered inefficient. In most patients, therapy directed at reducing nitrogen absorption such as protein restriction,[10,35] oral neomycin,[6,10,16,35] lactulose,[6] and colonic exclusion or lowering plasma ammonia levels has been generally unrewarding.[20,25,30,32] At best, these measures prevented or decreased the numbers of encephalopathic episodes.[19,23] Even so, progressive paraparesis was observed even when encephalopathy was effectively averted. Oral lioresal may be tried to improve mobility with decreased spasticity, although the effectiveness is not confirmed.[20,30] The effectiveness of Orthotopic Liver Transplantation (OLT) has not yet been determined. To date, there were only 15 cases undergone OLT in the English literature. Although the first HM receiving an OLT was reported to have no appreciable improvement in his neurological symptoms or signs despite normalization of his liver function,[11] some appending case studies have reported altogether 11 cases showing quite impressive improvement,[18,21,24-26] mostly recovered to be ambulatory. The duration of clinical manifestations of HM before OLT may be the main factor affecting the therapeutic outcome. Liver transplantation should be considered as the first therapeutic option and should be performed before spinal cord damage becomes irreversible. This also implies that the spinal cord damage is irreversible at the end stage, which is compatible with the axonal loss seen at necropsy in some cases.[30]

CONFLICTS OF INTEREST

The authors have no potential conflicts of interest to be disclosed.

CONSENT

The patient has provided written permission for publication of the case details.

ACKNOWLEDGEMENT

This study was supported in part by Guangdong Province Technological Grant 2007B031502003, Guangzhou City Technologi-

cal Grant 2009ZL-E021, and National Natural Sciences Foundation of China Grant 30971028 (Hua Hong).

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ISSN 2379-4038 Open Journal http://dx.doi.org/10.17140/LROJ-1-108

SUPPLEMENT MATERIALS

Time	Author	Age	Sex	Etiology	Surgical Shunt	Type	Sponta-neously Shunt	Type	Shunt History(mo)	HE/Before Or After	Progres-sion Time(mo)	EDSS disability scale*	Involvement of the Upper Limbs	Superficial Sensation Deficit	Deep Sensation Deficit	Sphincter Incontinence	non-Pyramidal Manifes-tation	Blood Ammonia Elevated	Brain MRI Abnormal-ity
1949	Leigh AD et al	50	M	CC	UK	UK	UK	-	UK	Yes/After	UK	UK	UK	UK	Yes	Yes	UK	UK	UK
1960	Zieve L et al	53	M	AC	Yes	PCS	UK	-	36	Yes/Before	UK	3	No	No	No	Yes	No	Yes	UK
		38	M	CC	Yes	PCS	UK	-	54	Yes/Before	3	3	No	No	No	Yes	No	UK	UK
1964	Scobie BA et al	63	M	AC	Yes	PCS	Yes	Other	UK	UK/-	UK	1	No	No	No	Yes	dysarthria	Yes	UK
1964	Drake A et al	54	M	AC	Yes	PCS	UK	-	72	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
1966	Liversedge LA et al	42	M	UK	Yes	PCS	UK	-	12	No/-	UK	2	No	UK	UK	UK	No	UK	UK
		45	M	CC	No	-	Yes	UK	UK	Yes/After	UK	3	No	UK	UK	UK	dysarthria, tremor	Yes	UK
		33	M	UK	Yes	PCS	UK	-	4	No/-	6	3	Yes	UK	UK	UK	No	UK	UK
		37	M	CC	Yes	PCS	UK	-	12	Yes/Before	UK	UK	No	UK	UK	UK	No	UK	UK
		41	M	UK	Yes	SRS	UK	-	72	Yes/UK	UK	3	Yes	UK	Yes	UK	dysarthria, ataxia	UK	UK
		41	M	UK	No	-	UK	-	-	No/-	UK	1	No	UK	UK	UK	dysarthria, ataxia	Yes	UK
1968	Pant SS et al	48	M	AC	No	-	UK	-	-	Yes/UK	24	1	No	No	No	No	No	Yes	UK
		53	M	AC	Yes	PCS	UK	-	6	Yes/Before	UK	3	No	No	No	No	No	Yes	UK
1969	Krishnaswami V et al	33	M	UK	Yes	PCS	UK	-	10	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
1970	Bechar M et al	31	M	CC	Yes	SRS	UK	-	20	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
		31	M	CC	Yes	PCS	UK	-	6	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
		29	M	CC	Yes	SRS	UK	-	72	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
1972	Lefer LG et al	40	M	BC	Yes	SRS	UK	-	5	Yes/After	UK	3	No	No	No	No	No	Yes	UK
1975	Gauthier G et al	62	M	CAH	Yes	PCS	UK	-	18	UK/-	UK	UK	UK	UK	UK	UK	UK	UK	UK
1976	Mousseau R et al	53	F	AC	No	-	Yes	Other	UK	Yes/Before	UK	2	No	No	No	No	No	No	UK
1978	Robinson CE et al	37	M	AC	Yes	PCS	UK	-	20	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
1979	Budillon G et al	19	M	AC	Yes	PCS	UK	-	36	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
1982	Cosnett JE et al	18	UK	AC	Yes	SRS	UK	-	24	No/-	UK	UK	No	UK	UK	UK	UK	UK	UK
		17	UK	AC	Yes	SRS	UK	-	96	Yes/Before	UK	UK	No	UK	UK	UK	UK	UK	UK
1983	Sarin SK et al	42	F	IPH	Yes	SRS	UK	-	34	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
1984	Sage JI et al	61	M	AWC	No	-	No	-	-	No/-	24	UK	No	No	Yes	No	No	No	UK
		63	M	AWC	No	-	No	-	-	No/-	48	UK	No	No	Yes	No	No	No	UK
		56	F	AWC	No	-	No	-	-	No/-	2	UK	No	No	Yes	No	No	No	UK
		53	M	AWC	No	-	No	-	-	No/-	24	UK	No	No	Yes	No	No	No	UK
		63	M	AWC	No	-	No	-	-	No/-	12	UK	No	No	Yes	No	No	No	UK
1985	Lebovics E et al	52	M	AC	Yes	PCS	UK	-	60	Yes/Before	UK	2	No	No	Yes	No	No	No	No
		67	M	BC	Yes	PCS	UK	-	14	Yes/Before	UK	2	No	No	No	No	No	No	UK
1985	Giangaspero F et al	60	M	AC	Yes	PCS	UK	-	13	Yes/Before	UK	3	No	No	No	No	dysarthria	Yes	UK
1985	Rab SM et al	40	M	CC	Yes	PCS	UK	-	25	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
		60	F	UK	No	-	No	-	-	Yes/Before	UK	UK	UK	UK	UK	UK	UK	UK	UK
1991	Bain VG et al	39	F	AC	Yes	PCS	UK	-	96	Yes/Before	UK	3	No	UK	UK	UK	UK	UK	UK
1992	Demirci M et al	45	M	CHF	No	-	Yes	Other	UK	Yes/Before	6	2	No	No	No	No	dysarthria , ataxia	Yes	UK
1992	Anand BA et al	30	M	IPH	Yes	PCS	UK	-	121	Yes/Before	UK	UK	No	UK	UK	UK	ataxia	UK	UK
1993	Bourgeois S et al	24	M	AC	No	-	No	-	-	Yes/After	1	UK	Yes	No	No	No	No	Yes	Yes
1993	Tsuchiya K et al	46	F	AWC	UK	-	UK	-	-	No/-	2	UK	No	No	No	No	ataxia	UK	Yes
		58	M	AWC	UK	-	UK	-	-	No/-	4	UK	No	No	No	No	No	UK	Yes
1994	Sobukawa E et al	76	M	PHC	No	-	UK	-	-	Yes/After	1	3	No	No	No	No	No	Yes	No
1994	Mendoza G et al	44	M	AC	Yes	PCS	UK	-	24	Yes/Before	2	2	No	No	No	No	No	UK	UK
		66	M	AC	Yes	PCS	UK	-	36	Yes/Before	2	3	No	No	No	No	No	UK	Yes
		61	M	PHC	Yes	PCS	UK	-	12	Yes/Before	18	3	No	No	No	No	No	UK	No
1996	Counsell C et al	52	M	AC	No	-	Yes	Other	UK	Yes/Before	1	2	No	No	Yes	No	No	No	No
1996	Campellone JV et al	35	M	IPH	Yes	SRS	Yes	Other	396	Yes/After	84	2	Yes	Yes	Yes	No	tremor	Yes	Yes
1999	Troisi R et al	60	M	PHC	Yes	PCS	UK	-	132	Yes/Before	2	3	No	Yes	Yes	No	tremor	UK	UK
2000	Lewis MB et al	45	M	CHF	Yes	PCS	UK	-	324	No/-	12	1	No	No	No	No	dysarthria, tremor	Yes	Yes
2000	Spencer DC et al	UK	UK	AC	UK	-	UK	-	-	UK/-	UK	UK	UK	UK	UK	UK	UK	UK	UK
2000	Gospe SJ et al	14	M	CC	No	-	No	-	-	No/-	2	UK	No	Yes	No	No	No	No	Yes
2001	Yengue P et al	29	M	UK	Yes	SRS	UK	-	UK	UK/-	UK	UK	UK	UK	UK	UK	UK	UK	UK
2001	Wang MQ et al	41~56	3M 1F	PHC	Yes	TIPS	UK	-	2	No/-	UK	1	No	No	No	No	No	Yes	UK
				CC	Yes	TIPS	UK	-	1	UK/-	UK	UK	No	No	No	No	No	Yes	UK
				CC	Yes	TIPS	UK	-	3	UK/-	UK	UK	No	No	No	No	No	Yes	UK
				CC	Yes	TIPS	UK	-	5	UK/-	UK	UK	No	No	No	No	No	Yes	UK
2002	Obama R et al	48	F	UK	UK	UK	UK	-	UK	UK/-	UK	2	No	UK	UK	UK	No	UK	Yes
2003	Weissenborn K et al	35	M	PHC	No	-	UK	-	UK	Yes/UK	UK	2	No	No	No	No	dysarthria,ataxia,tremor	Yes	No
		40	M	PHC	Yes	TIPS	UK	-	19	Yes/Before	6	2	No	No	No	Yes	No	Yes	Yes
		42	M	PHC	Yes	TIPS	UK	-	9	Yes/Before	2	3	No	Yes	Yes	Yes	dysarthria,ataxia,tremor	UK	Yes
2005	Utku U et al	45	M	PHC	No	-	Yes	SRS	UK	No/-	6	2	No	No	No	No	No	Yes	No
		41	M	CC	No	-	Yes	SRS	UK	No/-	12	2	No	No	No	No	No	Yes	No
2005	Imai T et	35	M	AWC	No	-	No	-	-	No/-	48	UK	No	No	Yes	No	No	No	No
2006	Nardone R et al	39	F	BC	Yes	UK	No	-	UK	UK/-	UK	1	No	No	No	No	dysarthria	Yes	UK
		49	M	AC	No	-	Yes	UK	UK	UK/-	UK	1	No	No	No	No	No	Yes	UK
		54	M	PHC	Yes	UK	No	-	UK	UK/-	UK	1	No	No	No	No	No	Yes	UK
		60	M	PHC	Yes	UK	No	-	UK	UK/-	UK	1	No	No	No	No	No	Yes	UK
		64	F	AC	Yes	UK	No	-	UK	UK/-	UK	2	No	No	No	No	No	Yes	UK
		58	M	PHC	No	-	Yes	UK	UK	UK/-	UK	2	No	No	No	No	No	Yes	UK
2006	Panicker J et al	19	M	CC	Yes	SRS	Yes	SRS	24	No/-	24	2	No	No	No	No	No	Yes	No
2006	Conn HO et al	31	M	PHC	Yes	TIPS	UK	-	60	Yes/Before	UK	3	Yes	Yes	Yes	No	No	Yes	Yes
2007	Tazawa K et al	31	M	CTLN2	No	-	No	-	-	Yes/Before	12	2	No	No	No	No	No	Yes	No
2008	Koo JE et al	39	M	PHC	No	-	Yes	SRS	UK	No/-	3	2	No	No	No	No	ataxia	Yes	UK
		64	M	PHC	No	-	Yes	SRS	UK	No/-	6	2	No	No	No	No	No	Yes	UK
2009	Qu B et al	32	M	PHC	No	-	UK	-	-	Yes/Before	2	3	No	No	No	No	No	Yes	Yes
		29	M	PHC	Yes	TIPS	UK	-	8	Yes/Before	3	3	No	No	No	No	ataxia	Yes	Yes
2009	Yin YH et al	46	M	12/13 PHC	Yes	UK	UK	-	12	UK/-	3	UK	No	No	No	No	No	11/13 Yes 2/13 No	No
		60	M		Yes	UK	UK	-	144	UK/-	66	UK	No	No	No	No	No		No
		44	M		Yes	UK	UK	-	66	UK/-	48	UK	No	No	No	No	No		No
		18	M		Yes	UK	UK	-	18	UK/-	6	UK	No	No	No	No	No		No
		55	M		Yes	UK	UK	-	36	UK/-	24	UK	No	No	No	No	No		No
		41	M		Yes	UK	UK	-	36	UK/-	11	UK	No	No	No	No	No		No
		35	M		Yes	UK	UK	-	6	UK/-	3	UK	No	No	No	No	No		No
		67	F		Yes	UK	UK	-	108	UK/-	18	UK	No	No	No	No	No		No
		58	M		Yes	UK	UK	-	18	UK/-	9	UK	No	No	No	No	No		No
		48	M		No	-	UK	-	-	UK/-	36	UK	No	No	No	No	No		No
		51	M		No	-	UK	-	-	UK/-	18	UK	No	No	No	No	No		No
		45	M		No	-	UK	-	-	UK/-	7	UK	No	No	No	No	No		No
		50	M		No	-	UK	-	-	UK/-	8	UK	No	No	No	No	No		No
2009	Pinarbasi B et al	41	M	PHC	Yes	SRS	No	-	UK	Yes/Before	UK	UK	Yes	No	No	No	ataxia	Yes	Yes
		50	M	AC	No	-	Yes	SRS	UK	Yes/Before	UK	UK	No	No	No	No	No	Yes	Yes
		37	M	PHC	Yes	PCS	No	-	UK	Yes/Before	UK	UK	Yes	No	No	No	dysarthria, tremor	Yes	Yes
		48	M	PHC	No	-	Yes	SRS, RUV	UK	Yes/Before	UK	UK	No	No	No	Yes	No	Yes	Yes
		49	M	PHC	No	-	Yes	RUV	UK	Yes/Before	UK	UK	Yes	No	No	No	dysarthria	Yes	Yes
		56	M	CC	No	-	No	-	-	Yes/Before	UK	UK	Yes	No	No	No	No	Yes	Yes
		28	F	CC	No	-	Yes	ECV	UK	Yes/Before	UK	UK	Yes	No	No	No	dysarthria, ataxia	Yes	Yes
		31	F	PHC	No	-	Yes	ECV	UK	Yes/Before	UK	UK	Yes	Yes	No	Yes	ataxia	Yes	Yes
2010	Present Case	35	M	PHC	No	-	Yes	RUV	UK	No/-	2	2	No	No	No	No	No	Yes	No

*The detailed described patients were classified according to the EDSS disability scale. Patients who did not complain of neurological symptoms nor did objective examination reveal any were grade 0; Patients who have mild neurological abnormalities (hyperreflexia, extensor plantar responses) without disability were grade 1;Patients who experienced minimal disability (stiffness, nocturnal spasms and leg cramps)were grade 2; Patients who had neurological abnormalities (mild or moderate paraparesis) were grade 3.

Abbreviations: AC=alcoholic cirrhosis; AWC=alcoholism without cirrhosis; BC=biliary cirrhosis; CAH= chronic active hepatitis; CC=cryptogenic cirrhosis; CHF=congenital hepatic fibrosis; CTLN2=adult-onset type ii citrullinemia; ECV=enlarged coroner venous; F=female; HE=hepatic encephalopathy; HM=hepatic myelopathy; IPH=idiopathic portal hypertension; M=male; PCS=portocaval shunt; PHC= posthepatitic cirrhosis; RUV=recanalized umbilical venous; SRS=splenorenal shunt; TIPS=transjugular intrahepatic portosystemic shunt; UK=unknown

Supplement Table 1: Review on the clinical features of HM.

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time	author	Cerebral changes					Spinal cord							
		betz cell count decreased	cerebrum	globus pallidus	putamen		demyelination	the lateral pyramidal tracts	the ventral pyramidal tracts	the posterior columns (fasciculus gracilis)	spino-cerebellar tracts	axonal loss	secondary reactive changes	perivascular round cell infiltration
1949	Leigh AD et al	-	+	+	+		+	+	-	+	-	-	-	-
1960	Zieve L et al	-	+	+	+		+	+	+	+	-	-	-	+
1966	Liversedge LA et al	-	+	-	-		+	+	+	+	+	+	+	
1968	Pant SS et al	+	+	-	-		+	+	-	-	-	+	+	-
1968	Pant SS et al	+	+	-	-		+	+	-	+	-	-	+	-
1972	Lefer LG et al	-	+	+	+		+	+	-	+	-	+	+	+
1985	Giangaspero F et al	-	+	+	+		+	+	-	-	-	+	+	-
1994	Sobukawa E et al	-	-	-	-		+	+	-	-	+	-	+	-
2007	Tazawa K et al	-	+	+	+		+	+	-	-	-	-	+	

Supplement Table 2: Review on the pathological features of HM.

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