THE ADVOCATE'S GUIDE TO HEPATITIS C: A HANDBOOK OF SYMPTOMS AND THEIR CAUSES.

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Preface

The purpose of this guide is to aid those in the helping professions to better serve those with hepatitis C. The intended audience comprises advocates, paralegals, lawyers, nurses, physicians, social workers, psychologists, and others.

All too often, those trying to help people with hepatitis C are not sufficiently familiar with the particulars of the disease, nor with the multitude of complications and side effects hepatitis C can cause.

This guide assumes that the intended audience is already familiar with the basic issues surrounding disability benefits in British Columbia, and does not discuss the particulars of either the Canada Pension Plan Disability Program, the Provincial Disability Benefits Program, or the advocacy process.

Should you require more information on the particulars of advocacy or on the various disability plans available in British Columbia, we urge you to contact the BC Coalition of People with Disabilities, where you can obtain pamphlets, manuals and appeal kits. The BCCPD can be reached through their advocacy access line at 1-800 663-1278 or on the web at www.bccpd.bc.ca

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What is Hepatitis C ?

- Hepatitis C is a systemic disorder that primarily targets the liver, but can also trigger a host of autoimmune disorders and various other diseases, such as diabetes, non-Hodgkin's lymphoma, retinal complications and thyroiditis.
- It is caused by the hepatitis C virus (HCV). Hepatitis C was identified in 1989. Before 1989, this type of hepatitis was called non-A, non-B hepatitis, meaning that it was not caused by the viruses that produce hepatitis A or hepatitis B (two other viruses that can cause hepatitis).
- Often thought by the medical profession to be benign because the course of the disease is relatively slow, ***hepatitis C can kill*** by causing liver failure or liver cancer. For most people the progression to morbidity and mortality is slow (20-30 years); for others hepatitis C can cause cirrhosis and/or death more quickly.
- The way that hepatitis affects people varies from person to person. Some are not affected by the condition, but others are affected quite severely.

It currently seems that if 100 people acquire hepatitis C:

- 15-20 people will get rid of it within 2-6 months (much like we get rid of a flu virus)
- 60 people will have a long-term infection that may cause no problems or may cause levels of liver damage ranging from mild to serious.
- 20-25 people will have a long-term infection that leads to serious liver damage after 20 years. Of these people (i.e., those with serious damage after 20 years):
- 10-will remain stable and the other 15 will progress to liver failure or liver cancer after another 5 years. According to an article in *Gut* 2000;47:131-136, the 5-year rate for progression to hepatocellular cancer is 13.4% and the 5 year rate for progression to death is 15.3%.

Hepatitis C infection doesn't always make people sick. When someone does get sick, symptoms take a long time to develop (approximately 13 years). Symptoms often stay at a certain level and don't always get worse. They can come and go with no real pattern.

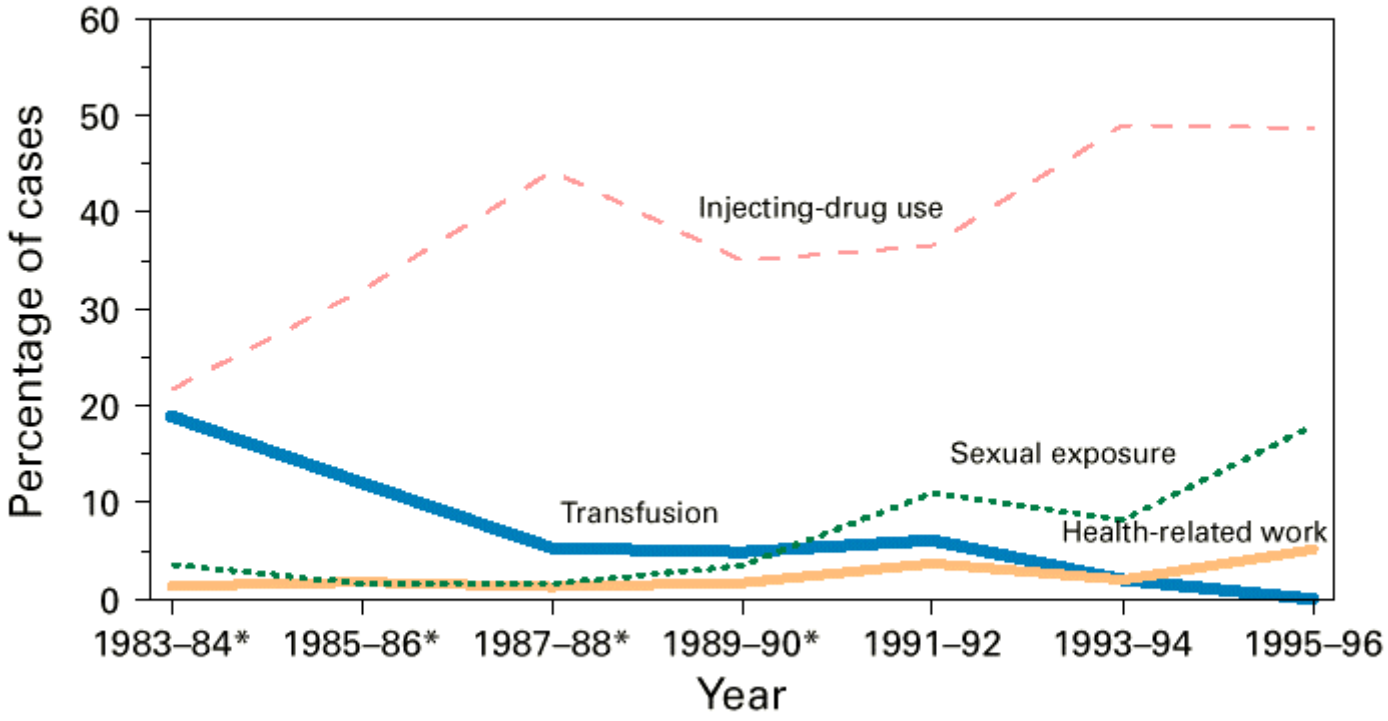
Some people with chronic infection don't have any noticeable liver damage or symptoms. These people remain well, but *they are infectious and should take care to reduce any risk of transmitting the virus to others*.

How is the Hepatitis C virus spread?

The virus is usually spread by direct contact with the blood of an infected person. This happens most often by:

- Sharing drug snorting or injection equipment such as needles and syringes;
- Having received a transfusion of blood or blood product in a country where the blood supply is not tested for hepatitis C. In Canada, this was thought to apply only to

FIGURE 1. Reported cases of acute hepatitis C by selected risk factors — United States, 1983–1996



*Data presented for non-A, non-B hepatitis.
Source: Centers for Disease Control and Prevention.

transfusions before 1990, since as of March 1990 all blood and blood products have been screened for the hepatitis C virus. However, infection through the blood supply—though rare—still occurs;

- Needlestick injuries;
- Sharing toothbrushes, dental floss, razors, nail files, or other items which could have trace amounts of blood on them;
- Skin piercing procedures, such as tattoos, body-piercing, acupuncture or electrolysis, if the equipment is not sterile;
- Infection through sexual intercourse is quite uncommon; however, the Canadian Minister of Health puts the risk of sexual transmission at somewhere around 2.5% over a twenty year period for those in monogamous relationships; or,
- An infected mother passing it to her newborn infant. Whether breast milk can transmit the virus is not yet known;

TRANSMISSION OF VIRAL HEPATITIS

	---A---	---B---	---C---	---D---	---E---
Food Borne	¥				¥
Fecal	¥				¥
Water Borne	¥				¥
Mollusk-Related	¥	¥			î
Intra-Family	¥	¥	î	¥	¥
Intra-Institutional		¥	¥		
I.V. Drug Use	î	¥	¥	¥	
Transfusion	¤	¥	¥	¥	
Hemodialysis		¥	¥	î	
Sexual	î	¥	O	¥	
Anal/Oral Sex	¥	¥			
Oral	¥	¤	î	î	¥
Household	¥	¥	î		
Maternal-Neonatal			¥	O	¥

¥ Confirmed transmission
¤ Rarely transmitted
î Suspected
O Uncommon
(courtesy of the American Liver Foundation)

Although a significant number (10-40%) of Hep C carriers don't know how they contracted the disease, avoiding these situations can help to prevent the spread of hepatitis C.

How common is Hepatitis C?

The total number of people in Canada who have hepatitis C is believed to be between 90,000 and 300,000. This means that up to one in every hundred people in Canada have hepatitis C. Most of these people have not been tested and do not know they have the disease. It is not possible to tell by looking at a person whether they have hepatitis C. All blood products and donors in Canada are now tested for hepatitis C. The rate of hepatitis C infection in transfused patients in Canada is now very, very low.

People at higher risk of having hepatitis C infection include:

- those who have used injection drugs;
- people who have received a blood transfusion or blood product before 1990; or
- people who have received an organ or tissue transplant before 1990.

Although information on hepatitis C in other countries, particularly in the developing world, is less available, there may be a higher risk in countries where the blood supply is not tested or

where contamination can occur through medical procedures. People who come to Canada from such countries, including internationally adopted children, should consider having HCV testing.

How can I tell if I have Hepatitis C?

After the hepatitis C virus infects your body, antibodies appear in your blood. A blood test can detect these antibodies and show if you have been infected with the hepatitis C virus. However, these tests do not show whether you are still carrying the virus in your body. So, if you have tested positive for the virus, assume you are infected and can infect other people.

What are the symptoms of Hepatitis C?

Some people feel well, have no symptoms and, therefore, don't know they have hepatitis C infection. Other people may have a brief illness with symptoms of hepatitis usually appearing six to nine weeks after they have been infected with the virus. Symptoms of acute hepatitis C infection may include: fever, tiredness, jaundice (yellow skin or eyes), abdominal pain, dark urine, loss of appetite, and nausea (sick to your stomach).

Other people will begin to experience long-term health concerns which are difficult to diagnose (for example, tiredness, confusion, continuous flu-like symptoms, inability to concentrate, muscle and joint pain, lack of energy, or digestive problems). Symptoms of hepatitis C have been confused with those of Chronic Fatigue Syndrome and Fibromyalgia (a disorder characterized by muscle pain, stiffness and easy fatigability). Recent studies show that hepatitis C can have a serious effect on the quality of life of those infected, severely affecting a person's ability to earn a living and to work full time.

Is there a Treatment for Hepatitis C?

People who test positive for hepatitis C should see their family doctor regularly and have their blood tested to see how their liver is functioning. They may also be referred to a specialist for further testing and assessment. Some people with hepatitis C may be offered treatment with anti-viral drugs, such as interferon. Increasingly we are coming to see those with advanced liver damage from hepatitis C requiring liver transplantation. *At this time, there is no vaccine to prevent people from getting hepatitis C infection.*

If you're diagnosed with hepatitis C, get informed. Check with your local support group. (If in doubt, call us at 250-361-4808).

Make sure that you:

- Get re-tested to confirm the diagnosis.
- Get vaccinated against hepatitis A and B
- Are sent to a specialist.
- Get copies of all tests.

The specialist should:

- Order an ultrasound yearly, if your family doctor didn't.
- Order an alphafetoprotein test yearly.
- Order a liver biopsy. (This is usually done by needle aspiration, but there are other options if there is a bleeding problem.)
- Discuss treatment options with you. (Get a second or even a third opinion if you don't agree.)

1. Fatigue and Hepatitis C

Taken from a factsheet compiled by HepCare, the Hepatitis C Case Management Trial (NSW, Australia).

Fatigue can be described as a sense of excessive tiredness, lack of energy or total body give out. The majority of people who have hepatitis C may at some stage experience fatigue although it must be stressed that it is not unusual for many people to experience periods of extreme tiredness which may relate to a busy lifestyle, stress or other factors. The term fatigue is commonly used for any symptom associated with tiredness. Fatigue specific to hepatitis C is not associated with the clinical entity known as Chronic Fatigue Syndrome (CFS). Fatigue may or may not be associated with over exertion or lack of rest, and may or may not be alleviated by rest. There is a wide clinical spectrum of fatigue. The mildest forms are where fatigue is experienced only through over-exertion or lack of rest, and responds well to rest. In its severe form, fatigue is not the result of either over-exertion or lack of rest, and in turn does not respond to rest.

Factors contributing to fatigue

- Liver dysfunction
- Chronic activation of the immune system
- Impaired liver function through alcohol, poor diet and other toxic substances
- Poor sleep and lack of rest
- Drug use
- Stress, distress and other situational problems
- Medical treatments such as interferon

Management of fatigue

In anyone who has hepatitis C, validation of fatigue symptoms is very important. An explanation as to why fatigue is experienced often relieves the stress caused by it to a certain degree. It is also important to be informed about the detrimental effects of alcohol, drug use, poor rest and poor lifestyle on liver function that will in turn contribute to increased fatigue. All of these lifestyle factors probably have a major impact on the immune system in addition to the virus itself. As well as adopting changes in behaviour and lifestyle which would maximize individual well-being and health, there are a number of tips to best manage the fatigue state so that the normal activities of daily living can be achieved without as much effort. Experiencing fatigue over a period of time can impact on many areas of life such as relationships, work or other activities. The management of fatigue may require some readjustment and professional help. In some cases it is important to consider some type of counselling support to assist in managing the fatigue which can cause people to feel quite depressed.

Interferon

While most people with hepatitis C are aware of Interferon as a drug treatment for hepatitis C, they may not be aware that this drug has been synthesised to match one of the naturally occurring interferons in the body. These are proteins produced by special cells which are made when the body recognises a foreign substance entering it. It acts as part of the protection mechanism against infection and is stimulated by a viral attack such as the flu virus. Interferon is actually the substance that seems to be the major factor in the flu-like symptoms and fatigue associated with hepatitis C.

So why does hepatitis C cause fatigue?

Fatigue does tend to be intermittent and mild, and in general, patients with more advanced chronic active hepatitis and raised liver function tests, (specifically higher ALT levels), tend to experience more severe symptoms of fatigue. However, this is not the rule and fatigue is not a reliable indicator or measure of disease progression or severity. Many people with hepatitis C experience some sort of fatigue and it is the most common single symptom. The cause of the fatigue experienced in hepatitis C has not been fully determined. There are probably multiple contributing factors towards this symptom and no one single factor can easily be studied without the influence of other factors. Also, the mechanism of how a disease state causes fatigue is not clearly understood.

There are two possibilities that could be contributing factors to the fatigue experienced in hepatitis C:

1. The Immune System

The major factor in chronic hepatitis C that may contribute significantly to fatigue symptoms is the continuing and long-term response of the immune system to the virus. It is generally accepted that the virus is both directly damaging to liver cells (the direct effect on other cells of the body has not been established) and indirectly damaging to the cells of the liver via the activity of the body's immune response to the virus. In other viral conditions such as measles, flu or hepatitis A for example, the response of the immune system rapidly produces antibodies, which eventually defeat the virus. The immune system, after clearing a virus such as measles returns to a less active state. In the majority of patients with hepatitis C (probably up to 75%), the immune system fails to have any impact.

2. The Metabolic Process of the Liver

The liver is the largest organ in the abdomen and is the centre of all metabolic processes that occur in the body. Liver disease of any kind interferes with the normal biochemical processes in the liver. The liver effectively acts as a filter for any toxic and unnecessary substance in the blood that may interfere with metabolic processes. It has a great deal to do with all substances that enter the body and a large proportion of the chemicals that are produced by other organs. This is why alcohol and certain other drugs are thought to have a strong bearing on the rate of disease progression in the liver. In chronic hepatitis any number of metabolic processes could be interfered with, resulting in the escape of toxic substances into the body. This has not been proven but fatigue symptoms have been seen to respond favourably to diets and herbal treatments which address this sort of toxic overload. The immune system is an intricate and

complex part of the whole individual and is intimately related to individual health. With the continuous and ongoing activity of the immune system and the related activity of certain chemicals and molecules as part of the immune response, there is understandably an ongoing effect on the well-being of the individual. The intermittent nature and unpredictability of this system could possibly be reflected by the individual nature of each person's immune response to the virus.

Herbals

Chinese and herbal medicines have been used with some success in the treatment of hepatitis C and the Traditional Chinese Medicine CH100 has been shown to significantly reduce the symptoms associated with hepatitis C including fatigue. Some formal trials have been done and certain combinations of herbs have been used in China, apparently successfully, for many years. When using herbals and liver tonics, it is recommended that you consult a certified herbalist or naturopath.

2. Fatigue as a Symptom of Liver Disease

Mark G. Swain, MD, Assistant Professor of Medicine, Hepatologist University of Calgary
SOURCE: Update on Liver Disease in Hepatitis Conference 1998

Learning Objectives: To understand what is currently known about fatigue in liver disease. To be familiar with the theories concerning the genesis of central fatigue.

Abstract:

A) What is Known About Fatigue in Liver Disease?

i) Viral Hepatitis Fatigue as a symptom which is commonly observed in patients seen in the clinic with chronic viral hepatitis, and fatigue can be incapacitating in some patients. However, the rigorous examination of fatigue as a symptom in viral hepatitis has only recently received scientific scrutiny. Anecdotally, fatigue has been reported to occur in approximately 5% to 10% of patients with hepatitis C and does not appear to be associated with the severity of the associated liver disease. Recently Davis showed that patients with hepatitis C had a reduced quality of life which did not appear to improve with viral clearance after a interferon treatment. Furthermore, Foster et al have documented, by using a validated questionnaire, that patients with hepatitis C have a significant impairment in their energy level. Interestingly, patients with chronic hepatitis B did not exhibit fatigue scores any different than control subjects. Hepatitis C patients with a history of intravenous drug abuse (IVDA) had worse fatigue scores than hepatitis C patients with no history of IVDA, but both groups had significant reductions in energy when compared with normal controls. Moreover, fatigue scores did not correlate with the severity of hepatitis as measured by hepatic histology or ALT.

ii) Cholestatic Liver Disease Fatigue, lethargy and malaise commonly occur in patients with the cholestatic liver diseases, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Fatigue occurs in up to 86% of patients with PBC3 and 75% of patients with PSC4 and has a significant impact on their quality of life. In PBC, fatigue constitutes the worst symptom in almost 50% of patients. Moreover, fatigue scores in 25% of PBC patients are similar to those documented in patients with multiple sclerosis. Fatigue in PBC does not correlate with disease severity. Fatigue in PBC is central, not peripheral, in origin.

B) Possible Mechanisms of Fatigue Genesis in Liver Disease

The specific cause(s) of central fatigue are poorly characterized; however, a number of causes of central fatigue have been suggested and investigated in patients with chronic fatigue syndrome. These theories identify sustained dysregulation of the stress response system which arise secondary to chronic physical and immune stress and which eventually lead to central changes characterized by blunting of the stress response. This blunting of the stress response has been repeatedly implicated in the genesis of fatigue in diseases characterized by chronic fatigue. These chronic stressors can be modified by psychological cofactors which modulate symptom development. These theories may be applicable to the genesis of central fatigue in patients with liver disease.

Liver disease constitutes a chronic uncontrollable stress to the patient. This chronic stress can be in the form of physical, emotional and/or immune stress. Furthermore, in experimental liver disease in rats we have identified a number of abnormalities in the central systems which control the stress response. Specifically we have identified decreased hypothalamic corticotropin-releasing hormone (CRH) levels and release in rats with cholestatic liver disease and this deficit in central CRH release leads to defective CRH-mediated behaviours in these animals. CRH is the main central activator of the stress response in rodents and humans and defective central CRH release has been implicated in the genesis of fatigue in the chronic fatigue syndrome.

In addition, we have identified augmented central responsiveness of cholestatic rats to the fatigue-ameliorating effects elicited by serotonin receptor activation (specifically 5HT1A receptors). Given that serotonin activates the stress response by stimulating central CRH release, these results are consistent with enhanced sensitivity to serotonin-induced CRH release in cholestatic rats as mediating the beneficial effects of serotonin receptor activation upon fatigue in these animals. Chronic immune activation leads to hypercytokinemia in patients with chronic liver disease. Prolonged exposure of the brain to elevated circulating cytokine levels can lead to a blunting of the stress response which has been implicated in the genesis of fatigue. We have identified elevated circulating cytokine levels in cholestatic rats and have also found a blunting of the activation of the stress response in cholestatic rats produced by acute immune activation and by exogenous cytokine administration. These results suggest that a blunting of immune activation of the stress response in liver disease may contribute to the genesis of fatigue in patients with chronic liver disease.

C) Treatment of Fatigue in the Patients with Liver Disease

i) Rule out Other Causes of Fatigue:
renal (BUN, Cr, lytes) · anemia (CBC) · electrolyte (Mg^{2+}, Ca^{2+}) · thyroid (TSH)

ii) Rule out Depression:
If patient is depressed consider treatment of depression and observe for improvement of fatigue

iii) Future Directions:
CRH agonists · centrally active serotonin receptor (5HT1A) agonists · anti-cytokines

References:

1,2. Davis GL, Balart LA, Schiff ER, et al. Assessing health-related quality of life in chronic hepatitis C using the Sickness Impact Profile. Clin Ther 1994;16(2):334-43.
3. Foster GR, Goldin RD, Thomas HC, et al. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology 1998;27(1):209-12.
4. Huet P-M, Deslauriers J. Impact of fatigue on quality of life of patients with primary biliary cirrhosis (PBC). Gastroenterology 1996;110:A1215.
5. Lindor KD, Wiesner RH, MacCarty RL, et al. Advances in primary sclerosing cholangitis. Am J Med 1990;89(1):73-80.
6. Jalan R, Gibson H, Lombard MG. Patients with PBC have central but no peripheral fatigue. Hepatology 1996;24:A162.
7. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4(3):134-53.
8. Tilg H, Wilmer A, Vogel W, et al. Serum levels of cytokines in chronic liver disease. Gastroenterology 1992;103(1):264-74.

3. Fatigue associated with chronic hepatitis C

Dr. Anthony Jones Hep C Review, Ed 30, Sept 2000

Is HCV fatigue a result of liver impairment, or are there other factors causing it?

Introduction

Many people with chronic hepatitis C develop severe fatigue that seems to be out of proportion to their general condition. The degree of fatigue does not appear to be related to the activity of the chronic hepatitis. In people with chronic hepatitis C, fatigue can be the main symptom, and is often the only symptom. It is a major determinant of their quality of life. Accordingly, it is important to determine the cause of fatigue, because such information will facilitate the development of effective treatments. A major problem in studying the effectiveness of new treatments for fatigue is that it is a perception and, consequently, subjective (one person's opinion). Therefore, fatigue is difficult to measure. Attempts are being made to overcome this problem by developing scales or scores of fatigue that employ objective criteria (things that are measurable).

To establish the effectiveness of a new therapy for fatigue it is necessary to compare the effects of a treatment and a placebo (dummy treatment) on an objective assessment of fatigue. In such a trial patients would be assigned to receive the treatment or placebo by chance with both the physician and the patient being unaware of the nature of their medication until the study has ended.

Fatigue

In addressing the problem of fatigue, peripheral fatigue should be distinguished from central fatigue. Peripheral fatigue occurs during prolonged exercise in working muscles and is unlikely to be particularly relevant to the fatigue experienced by most patients with chronic hepatitis C. Central fatigue, on the other hand, occurs as a consequence of changes in the brain. The question arises whether altered function of the brain in patients with chronic hepatitis C contributes to fatigue.

Causes of fatigue in chronic hepatitis C

Accumulating evidence suggests that certain complications of chronic liver disease are associated with altered transmission of nerve impulses in the brain. For example, pruritus (itching), which may complicate chronic hepatitis C, is associated with increased transmission of nerve impulses triggered by opioids (the body's own substances that have morphine-like effects), and poor concentration and sleepiness (which may occur as a late complication of chronic hepatitis C). Puritis is also associated with increased suppression of the activity of neurons (brain cells) as a consequence of enhanced inhibitory effects of the simple amino acid GABA (gamma-aminobutyric acid) on transmission of nerve impulses. Increased transmission of nerve impulses triggered by opioids in chronic hepatitis C may affect transmission of nerve impulses triggered by substances other than opioids. One of these additional substances that trigger nerve impulses is serotonin (5-hydroxytryptamine, 5-HT). Indeed, relief of itching in patients with chronic liver disease has been reported following administration of ondansetron into an arm vein. Ondansetron counteracts some of the nerve impulses triggered by serotonin by occupying a subtype of receptors for serotonin that are found on certain neurons. This finding suggests that this complication of chronic hepatitis C (itching) is associated with increased transmission of nerve impulses triggered by serotonin. Thus, altered transmission in serotonin pathways may occur in chronic hepatitis C and may contribute to behavioural complications of this disease, that may include fatigue. Accordingly, it is necessary to consider whether altered transmission of nerve impulses in serotonin pathways could contribute to fatigue associated with chronic hepatitis C. Three reports in the medical literature suggest that this could be the case. Firstly, the time that active male athletes could exercise on a bicycle for measuring exercise was significantly less after the administration of paroxetine (a drug that increases transmission of nerve impulses triggered by serotonin), than after administration of a placebo. The results could not be explained by extraneous effects of paroxetine on body functions. Paroxetine, which is used to treat depression, acts centrally on the brain. The authors of the study concluded that there may be "a central (brain) component to fatigue which is mediated by the activity of serotoninergic neurons (brain cells triggered to transmit nerve impulses by serotonin)". Secondly, in studies involving rats, fatigue during extended periods of exercise was reported to be related to indices of transmission of nerve impulses in the brain triggered by serotonin. Lastly, a woman with chronic hepatitis C and profound fatigue was reported to become completely free from excessive fatigue

when treated long-term with ondansetron 4 mg twice daily. While taking the drug she was able to work more efficiently and for longer hours.

Possible treatments?

The results of these three studies suggest that altered transmission of nerve impulses triggered by serotonin contributes to (central) fatigue originating in the brain. In particular, the findings in the case study suggest that altered transmission of nerve impulses triggered by serotonin - in neuronal pathways in the brain on which a specific subtype of serotonin receptors are located - contributes to the profound fatigue that commonly occurs in patients with chronic hepatitis C. Excessive fatigue associated with chronic hepatitis C may be amenable to effective treatment with drugs that act specifically on the serotonin system in the brain and alter transmission of nerve impulses triggered by serotonin. A controlled trial of oral ondansetron therapy for fatigue in patients with another chronic liver disease, primary biliary cirrhosis, has been initiated in Toronto, Canada.

References

1. Barkhuizen A, Rosen HR, Wolf S, Flora K, Benner K, Bennett RM. Musculoskeletal pain and fatigue are associated with chronic hepatitis C: a report of 239 hepoatology clinic patients. Am J Gastroenterol 94: 1355-1360; 1999.
2. Goh J, Coughlan B, Quinn J, O'Keane JC, Crowe J. Fatigue does not correlate with the degree of hepatitis or the presence of autoimmune disorders in chronic hepatitis C infection. Eur J Gastroenterol Hepatol l l: 833-838; 1999.
3. Elkins LE, Krupp LB, Scherl W. The measurement of fatigue and contributing neuropsychiatric factors. Semin Clin Neuropsych 5: 58-61; 2000.
4. Jalan R, Gibson H, Lombard MG. Patients with PBC have central but no peripheral fatigue. Gut 39 (Suppl 1): A30; 1996.
5. Jones EA. Fatigue associated with chronic liver disease: A riddle wrapped in a mystery inside an enigma. Hepatology 22: 1606-1608.
6. Jones EA, Bergsasa NV. The pruritus of cholestasis. Hepatology 29: 1003-1006; 1999. 7. Jones EA. Pathogenesis of hepatic encephalopathy. In: Pathophysiology of Liver Disease. Herrera J (Ed). Clinics Liver Disease 4: 467-485; 2000.
8. Jones EA, Yurdaydin C. Is fatigue associated with cholestasis mediated by altered central neurotransmission? Hepatology 25: 492-494; 1997.
9. Schworer H, Hartmann H, Ramadori G. Relief of cholestatic pruritus by a novel class of drugs: 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists: effectiveness of ondansetron. Pain 61: 33-37; 1995.
10. Wilson WM, Maughan RJ. Evidence for a possible role of 5-hydroxytryptamine in the genesis of fatigue in man: administration of paroxetine, a 5-HT re-uptake inhibitor, reduces the capacity to perform prolonged exercise. Exp Physiol 77: 921-924; 1992.
11. Bailey SP, Davis MJ, Ahiborn EN. Neuroendocrine and substrate responses to altered brain 5-HT activity during prolonged exercise to fatigue. J Appi Physiol 74: 3006-3012; 1993.
12. Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. Lancet 354: 397; 1999.

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4. Fatigue does not correlate with the degree of hepatitis or the presence of autoimmune disorders in chronic hepatitis C infection.

AUTHOR: Goh J, Coughlan B, Quinn J, O'Keane JC, Crowe J, Department of Hepatology, Mater Misericordiae Hospital and University College Dublin, Ireland. *SOURCE: Eur J Gastroenterol Hepatol 1999 Aug;11(8):833-8*

BACKGROUND:

Fatigue is probably the most commonly reported symptom in chronic hepatitis C virus (HCV) infection. It is unclear whether fatigue is related to the severity of underlying liver disease or other autoimmune disorders often described with chronic HCV infection.

OBJECTIVE:

To quantify fatigue in terms of its impact on quality of life in a homogeneous cohort and examine its relationship to the status of liver disease or associated autoimmunity.

METHODS:

The Fatigue Impact Scale (FIS) questionnaire (Fisk et al. Clin Infect Dis 1994; 18:S79-S83), a recently validated psychometric tool for assessing patients' perceptions of the functional limitations attributable to fatigue (40 statements; three subscales: physical, cognitive and psychological; maximum score = 160), was applied to a cohort of Irish women who were PCR-positive for HCV genotype 1b via inoculation with contaminated anti-D products in 1977. RIBA-positive, PCR-negative patients (n = 20) and healthy age-matched women (n = 50) served as controls. The degree of hepatitis was assessed using the Knodell histological activity index (HAI) score on previous liver biopsies. Clinical and laboratory evidence of cryoglobulinaemia, Sjogren's syndrome, connective tissue diseases, autoimmune thyroid disease and glomerulonephritis was sought.

RESULTS:

The mean FIS score of the 66 PCR-positive women (mean 78+/-36; range 7-153) was significantly higher than in age-matched controls (mean 31+/-24, range 0-78, $P<0.001$) but not statistically different from that of the RIBA-positive, PCR-negative group. The FIS score did not correlate with the HAI score (median HAI = 4; range 2-9; Pearson's correlation coefficient $r=0.01$, $P=0.9$). Significant levels of cryoglobulins were detected in 10 (15.2%). The sicca complex was diagnosed in six patients, three of whom had associated cryoglobulinaemia. Thyroid antibodies, anti-nuclear antibody, rheumatoid factor, antimitochondrial antibody and anti-smooth muscle antibody were detected in 15.2%, 6%, 4.5%, 4.5% and 1.5%, respectively. There was no significant difference in the FIS score between the groups with autoimmune diseases and those without. The FIS score of the nine patients previously treated with interferon was not statistically different from the untreated group ($P=0.39$). **CONCLUSION:** The perceived functional impact of fatigue on quality of life is significantly higher in patients with chronic HCV genotype 1b infection compared to healthy controls. However, it is unrelated to the degree of hepatitis and cannot be accounted for by the co-existence of autoimmune disorders alone.

5. Hep C Illness - Outside the Liver (Extrahepatic)

By Paul Harvey, The Hep C Review, Ed30, Sept 2000.

In considering the possible impact of hepatitis C on our health, we should first question our definition of good health. Some clinicians suggest that good health is not so much a specific state such as "absence of disease or illness". They believe that good health is an overall approach: one that accommodates a certain level of illness as normal and has people working positively towards overcoming the physical and emotional problems caused by disease (Lorig et al.). This is quite a useful approach when considering that most people will develop some type of chronic illness in their life.

Our complex biological system

An additional issue before examining the possible impact of hepatitis C on health is consideration of the incredibly complex biological nature of our bodies. Modern technologies are forever changing our world but they remain crude in comparison to the fantastic interaction of electrical, chemical and biological processes that exist within us. Given this level of complex interactions, it is not unusual that a disease most noticeably causing illness in one major organ or body system will have some level of impact on other parts of the body.

Non-liver HCV illness

Studies suggest that hepatitis C related fatigue is not primarily related to actual liver disease but is linked either to disorders of the immune system (Eur J Gastro Hept 1999 Aug;11(8):833-8) and (Am J Gastro 1999 May;94(5):1355-60), or to altered neurotransmission (brain tissue) function (Lancet 1999 Jul 31;354(9176:397). The most commonly reported symptom of hepatitis C is fatigue. Clinicians are yet to confirm if this is an extrahepatic condition (an illness affecting parts of the body other than in the liver), or if it is related to actual liver damage (see p16). Aside from fatigue and possible complications of actual liver damage, hepatitis C infection has comparatively little impact on the rest of our body - although several conditions have been observed. Of the range of other health conditions linked to hepatitis C, some have been observed and well documented by clinicians (see below), while the occurrence of many others have been noted in only a small number of cases and may yet be explained as simple coincidence.

The publication *Hepatitis C: a management guide for general practitioners* (Aust Family Physician 1999;28 SI:27-31) recently listed a range of HCV extrahepatic conditions (right). Many of these are reported in this edition of The Hep C Review by Dr Bryan Speed (page 12), Dr Tony Jones (page 16), Doug Mellors (page 29), Dr Ed Gane (page 30) and Tina Pirola (page 34).

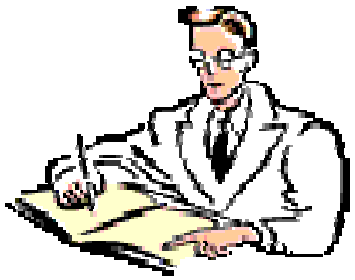
- Arthralgia
- Cryoglobulinemia
- Diabetes mellitus
- Glomerulonephritis
- Lichen planus
- Non-Hodgkin's lymphoma
- Peripheral neuropathy

- Porphyria cutanea tarda
- Sicca syndrome
- Sjogren's syndrome
- Thrombocytopaenia
- Thyroid disorders
- Vasculitis

Summary

The majority of all people in our culture experience chronic illness at some point in their life. So although it's great to have good health, it's probably unreasonable to expect to have perfect health. In a small number of cases, hepatitis C can cause imbalance and illness in various parts of the body - other than the liver. Given the complexity of our bodies, the fact that such extra hepatic HCV conditions can occur should not be seen as abnormal. These "extra hepatic conditions" are not necessarily serious and properly diagnosed and treated, they should not cause alarm if they occur. Certainly, they do not warrant unnecessary anxiety. If anyone suspects they may be experiencing extra hepatic conditions, they should consult their GP and if necessary, ask for referral to a hepatologist or other hepatitis specialist. Prior to such consultation, people should do a "work up" with their doctor; i.e., noting the frequency of possible symptoms and having any relevant blood tests done.

Paul Harvey is Special Projects Officer with the Hepatitis C Council of NSW.



6. Hepatitis C and Depression

By Doug Mellors. Doug Mellors is a psychologist and keen supporter of the Hepatitis C Council of South Australia. Abridged from an original article that previously appeared in both The Hep C Review (June 1998) and the bi-monthly newsletter of the Hepatitis C Council of South Australia, Hep C Community News (April 1998). Taken from the Hep C Review, Ed 30, Sept 2000

Not everyone with hepatitis C suffers from depression and in those cases where they do, it is difficult to pinpoint the cause. A question many people ask is: does being infected with hepatitis C cause depression—or is depression a reaction to being diagnosed as hepatitis C positive?

What is depression?

Depression is a disturbance of mood. The assessment, diagnosis and treatment are based on the severity, frequency and duration of symptoms reported by the person. There are no tests for depression although there are a number of particular questionnaires that are sometimes used to assess it.

What are the symptoms of depression?

There are a number of different types of depression but some general symptoms are: feelings of despair, a sense of worthlessness, the inability to take pleasure from the things one usually enjoys, feelings of guilt, sleep disturbance, tiredness, ruminating on gloomy or negative thoughts, social withdrawal. People with severe depression are often immobilised by it and tend to isolate themselves socially and neglect their surroundings and personal appearance. Thoughts of suicide are quite common in people with severe depression.

What causes depression?

The exact cause of depression is unknown and it is more likely due to a number of factors interacting with each other, rather than to any single factor. However, it is generally accepted that the symptoms are due to chemical changes in the brain which influence mood. When a person is depressed these chemicals - called neurotransmitters - are not manufactured in sufficient quantity to keep one's mood balanced. What causes this chemical imbalance is not clear, but may be related to: a family history of depression or alcoholism, early parental loss or neglect, recent negative life events, a critical or hostile spouse, lack of a close confiding relationship, lack of adequate social support and long-term lack of self esteem. It is important not to confuse depression with feeling "blue" or having a low mood. Feeling blue is a normal reaction to a sad experience and is usually transient.

What about depression in people with hepatitis C?

It can be seen from the above descriptions of the symptoms of depression that some of them are similar to those of hepatitis C (e.g., tiredness, sleep disturbance and loss of appetite) which makes the diagnosis of depression more difficult. While these symptoms of hepatitis C are thought to be related to chemical changes or imbalances in the body there is no evidence at present that these chemical changes interfere with brain chemistry and result in depression. What

clinicians do know is that being diagnosed with an incurable and life-threatening illness is likely to trigger depression in some people.

What are the treatments for depression?

There are many treatments for depression. Outlined here, are only two. Both are well-researched. The first is treatment with anti-depressant medication. The aim of this treatment is to restore the chemical imbalance by drugs which affect neurotransmitters in the brain. In the last five years many new types of anti-depressant medications have been developed due to improved understanding of chemical interactions in the brain. These new anti-depressants (of which Prozac is only one) are much better tolerated than those of the previous generation of anti-depressants. They have much better response rates and fewer side-effects e.g. drowsiness, constipation and loss of libido. The second treatment for depression is called Cognitive/Behavioural Therapy and is a non-drug psychological treatment. The Cognitive part of the therapy relates to a person's thoughts. The role of the therapist is to teach the person how to recognise and monitor their negative thoughts; how to challenge these thoughts and replace them with positive ones. The behavioural part of the therapy relates to what activities the person is involved in on a day-to-day basis. The therapist asks the person to keep a record of their daily activities and how they feel about them. The therapist encourages the person to increase those activities which they enjoy - especially when they involve social interaction.

Which treatment for depression works best?

Studies on outcomes of different therapies show little difference between anti-depressant medication and cognitive/behavioural therapy. In general they suggest that if you have mild to moderate depression it may be better to try a non-drug therapy first and commence antidepressants if it does not work. With severe depression it is probably better to start with anti-depressants first and consider non-drug therapies as an additional part of the treatment.

7. Impaired Health-Related Quality of Life in Chronic Hepatitis C: The How, but Not the Why

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Hepatology, January 1999, p. 277-279, Vol. 29, No. 1

During the past decade, patient-based health outcomes research has become a growth industry. Its data are being merged with clinical and economic databases to inform health care decision-making. Supported by a variety of health care organizations, accrediting bodies, employers, health policy strategists, and an expanding coterie of investigators, outcomes research seeks to assess the health of populations and the value of health care interventions as reflected in measurable changes in outcomes. With increasing emphasis on the patient as the focal point of health care, preservation of functioning and well-being is viewed as the principal goal of medical care and, of course, is best evaluated by the patient. As a consequence, measurement of patient-based assessment of health-related quality of life (HRQOL) is now an important focus of outcomes research.

However, the term and concept of "quality of life" has been problematic.1 Quality of life is generally defined as an individual's overall satisfaction with life and general sense of well-being and includes elements regarding health, personal accomplishments and resources, life situation, spirituality, level of activity, and social support.2 HRQOL may be more narrowly and specifically defined. It focuses on self-perceived health and well-being domains. These include assessments of physical function, somatic sensation, psychological status, social interactions, functional capacity, and sense of well-being as influenced by health status. Each of these is subjective, based entirely on the perception of the individual, and usually self-reported. No objective functional testing or assessment is included. HRQOL in patients may also be defined by the nature and intensity of symptoms of the responsible disease and those attributable to its treatment. From a patient's perspective, important outcomes of health interventions include the elimination or reduction of symptoms, if present, improved health-related quality of life, and restoration of normal life expectancy. Although its proponents would suggest that HRQOL is the outcome patients care most about, one wonders perhaps as one ages whether restoration of life expectancy might be an even higher priority, at least for some.

It is by no means surprising that chronic hepatitis C, the dominant liver disease of our era, has become the subject of HRQOL studies. This has been prompted by the high prevalence of the disorder and major uncertainties about its impact on functional status and well-being. A variety of instruments for assessing HRQOL have been used in chronic hepatitis C. The most familiar one is the SF-36 (short form-36) questionnaire, currently the principal generic tool used in reporting quality of life changes by managed care plans and the one most frequently used in clinical trials of a variety of interventions in a number of disorders. The SF-36 permits rapid measurement; is reasonably easy to administer, score, and interpret; and has been shown to have acceptable construct, criterion, and known-groups validity for many disorders. In addition to its good psychometric characteristics, it is reproducible over time in stable patients, is generally responsive to meaningful interventions and clinical changes, and correlates with patient and

health care provider global ratings. Its psychometric characteristics in chronic hepatitis C are presumed to be similar.

Based on responses to SF-36, Foster et al. showed in an English study that noncirrhotic patients with chronic hepatitis C had significantly reduced scores for all dimensions assessed by this tool and that scores were poorer than those reported by patients with chronic hepatitis B.3 Only 72 patients participated in this study, and treatment effects on HRQOL were not evaluated. Hunt et al. used, in addition to the SF-36, the Beck Depression Inventory and the Hospital Anxiety and Depression Scale in an even smaller study of 38 patients with chronic hepatitis C.4 The presence of cirrhosis did not influence scores on any of these scales and no differences between interferon responders and nonresponders were found at completion of therapy. However, responders described fewer emotional problems and a lower prevalence of anxiety after treatment.

In this issue, my colleague at the University of Massachusetts, Herb Bonkovsky, and his coworkers have provided convincing evidence, in the largest available data set comprised of evaluations by 645 patients, that the health burden perceived by patients with chronic hepatitis C is considerable. HRQOL was assessed at baseline and 24 weeks after ending interferon therapy with SF-36 and additional items that evaluated perceptions of appetite, cognitive functioning, current health status, feelings of health distress, sexual functioning, and sleep quality. The data indicated that at baseline patients scored low on all measured domains whether or not cirrhosis was present. Simply stated, patients rated their physical and mental health, functional health, and well-being as poor. And compared with a healthy population, the greatest reductions were found in those scales that reflected physical impairment. Of interest was the observation that baseline scores of sustained responders to treatment with interferon alfacon-1 did not differ from those of nonresponders. This suggests that HRQOL scores before treatment should not be used to predict the likelihood of a sustained response to treatment. The finding that HRQOL scores improved in those patients who were sustained biochemical or virological responders is critically important and supports the concept that the diminished HRQOL in chronic hepatitis C is, at least in part, a consequence of the disease. It may not be the entire story because the improvement in HRQOL scores noted in responders were still lower than those of the healthy controls. The potential psychological impact of knowledge of an objective "response" to therapy on perception of health status is thoughtfully addressed. While it would have been difficult not to inform and certainly unethical to mislead patients about their biochemical or virological response to interferon therapy, one must wonder about the possible role played by giving this information to patients.

Although it might have been interesting to have the patients assess their HRQOL during treatment, it seems almost obvious that HRQOL would deteriorate given the adverse event profile of interferon therapy and, for that matter, although not studied here, combination therapy with interferon and ribavirin. It would have been helpful to collect post-treatment data at more than one time period to determine whether improvement in HRQOL persists over time in the responders and whether any changes occur in the nonresponders. Is there a delayed, long-term HRQOL benefit of treatment in nonresponding patients?

Because neither the SF-36 nor the additional items used by Bonkovsky et al. to assess HRQOL in chronic hepatitis C have established sensitivity in detecting small but clinically important changes in chronic hepatitis C with or without treatment, more sensitive, disease-specific

instruments may need to be developed for assessing the impact of interventions. Such instruments would have to be patient- and data collector-friendly. A 69-item questionnaire, which includes all 8 scales of the SF-36 and 9 other generic and hepatitis C-specific health concepts, has been developed as such an instrument.5 This instrument performed well on psychometric testing. In the initial testing, the patient sample consisted of 157 patients who qualified for inclusion in randomized trials of interferon treatment. Similar to the data of Bonkovsky et al., chronic hepatitis C patients scored poorly on the generic scales when compared with a healthy population and patients with hypertension. Patients with chronic hepatitis C also scored worse than type II diabetics on measures of bodily pain, vitality, social functioning, health distress, and sleep somnolence. The presence of one or more of a broad and obviously nonspecific set of physical findings (ranging curiously from hepatomegaly and spider angiomas to parotid enlargement and Dupuytren's contractures) was correlated with lower generic and disease-specific scale scores. I find this a bit peculiar given the closer association of parotid enlargement and Dupuytren's contractures with alcoholism rather than with hepatitis C virus-related disease. In this study only the physical functioning and bodily pain scales were linked to the presence of cirrhosis and alanine transaminase levels fivefold greater than the upper limit of normal. Further evaluation of this tool in untreated and treated patients is eagerly awaited.

Of course, it should be immediately obvious that patients participating in each of the cited studies may not fully represent the universe of patients with chronic hepatitis C. The patients studied had been diagnosed and told that they had chronic hepatitis C. They were referred to and seen at medical centers and had to be willing to participate in randomized, controlled clinical trials requiring multiple visits, venipunctures, and liver biopsies. Perhaps they were motivated to seek expert opinion because they felt less well than other patients for whom the infection or the disease is not causing changes in health perceptions. It is also possible that their subjective health perceptions had been greatly influenced by their familiarity with anecdotal gloomy assessments of the disease on the Internet or inaccurate descriptions of the disease and its treatment in popular media. It is also unclear what influence the referring primary care physician or gastroenterologist/hepatologist had on the patient's perception of his or her health. Does attendance at a hepatitis support group affect such perceptions? Although these factors might influence patients to lower their ratings of their own health, it is also possible that the study population does not represent patients whose very apparent low levels of health and functioning excluded them from participation in a therapeutic trial. Exclusion of such patients would diminish the differences between the scores for the chronic hepatitis C patients versus the healthy population.

What might prove interesting would be to measure HRQOL in recently diagnosed patients, before they receive an explanation of the disease. Repeating the measurement on follow-up, before treatment but after they have been educated, might help sort out the influence of information on health perception in chronic hepatitis C. This difficult task will become possible when HRQOL instruments become a component of routine health assessment and when screening for hepatitis C virus infection becomes commonplace.

The reported observations on HRQOL in chronic hepatitis C need to be incorporated into cost effectiveness analyses to permit more valid assessments of the utility values for different health

states used in deriving quality-adjusted life years. Thus far, these assessments have been undertaken by physicians and nurses rather than by patients. It would have been interesting to compare and correlate physician's assessments with those of the patients in these studies.

In summary, Bonkovsky et al. have clearly shown that HRQOL is broadly impaired in chronic hepatitis C and improves in those who respond to interferon treatment. They do not, however, directly address the mechanisms underlying this impairment. What is it about this disease that impairs the subjective health perceptions of these patients? How does persistent hepatitis C virus infection impair one's sense of well-being? Is it simply the presence of viremia, or is it other pathophysiological events occurring as a result of the infection, such as the release of cytokines or the induction of specific noxious hepatic proteins or other materials? What is the role of hepatocyte necrosis or inflammation in this process? Is there some sort of neuropsychological impairment as a consequence of the disease that affects patients' perceptions of health? Answers to these questions will permit a better understanding of the pathogenesis of chronic hepatitis C and may lead to the development of specific therapies directed to improving our patients' sense of well-being, eradicating the infection, and restoring health.

Abbreviations

Abbreviations: HRQOL, health-related quality of life; SF-36, short form-36.

REFERENCES

1. Leplege A, Hunt S. The problem of quality of life in medicine. JAMA 1997;278:47-50[Medline].

2. Diener E, Suh E. Measuring quality of life: economic, social, and subjective indicators. Soc Indicators Res 1997;40:189-216.

3. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. HEPATOLOGY 1998;27:209-212[Abstract/Full Text].

4. Hunt CM, Dominitz JA, Bute BP, Waters B, Blasi U, Williams DM. Effect of interferon-alpha treatment of chronic hepatitis C on health-related quality of life. Dig Dis Sci 1997;42:2482-2486[Medline].

5. Bayliss MS, Gandek B, Bungay KM, Sugano D, Hsu M-A, Ware JE Jr. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. Qual Life Res 1998;7:39-55[Medline].

8. Musculoskeletal pain and fatigue are associated with chronic hepatitis C: a report of 239 hepatology clinic patients.

Am J Gastroenterol 1999 May;94(5):1355-60
Barkhuizen A, Rosen HR, Wolf S, Flora K, Benner K, Bennett RM

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OBJECTIVE:

The aim of this study was to identify the frequency of fatigue and musculoskeletal pain in hepatitis C compared with other liver diseases.

METHODS:

Hepatology outpatients were evaluated by questionnaire for musculoskeletal pain and fatigue. Charts were reviewed for diagnoses, aminotransferases, histology, treatment, and presence of hepatitis C by second generation ELISA and/or polymerase chain reaction. The frequency of symptoms in patients with and without hepatitis C were compared.

RESULTS:

In 239 patients (mean age 46.7 +/- 11.6 yr; 52% male) musculoskeletal pain was present in 70% for 6.7 +/- 8.3 yr and fatigue in 56% for 3.3 +/- 5.1 yr. Backache was the most common complaint (54%), followed by morning stiffness (45%), arthralgia (42%), myalgia (38%), neck pain (33%), pain "all over" (21%), and subjective joint swelling (20%). Diffuse body pain was present in 23% on a pain diagram and was strongly associated with fatigue. There was a significant association between hepatitis C positivity and the presence of musculoskeletal pain (81% of HCV-positive compared with 56% of HCV-negative patients, respectively; $p = 0.0001$), and fatigue (67% compared with 44%; $p = 0.001$). Musculoskeletal pain was more frequent among patients with isolated hepatitis C infection than among patients with isolated hepatitis B or alcoholic liver disease (91%, 59%, and 48%, respectively; $p = 0.004$). Similarly, fatigue was more frequent among patients with isolated hepatitis C than among those with isolated alcoholic liver disease or hepatitis B (66%, 30%, and 29%, respectively; $p = 0.004$). There was no relationship between musculoskeletal complaints and possible route of acquiring hepatitis C, levels of aminotransferases, liver disease severity on biopsy, or interferon treatment.

CONCLUSIONS:

Musculoskeletal pain and fatigue are frequent in hepatology clinic attendees, particularly those with hepatitis C and are unrelated to severity of liver disease, route of infection, or interferon therapy. PMID: 10235218, UI: 99249297

9. Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review.

Am J Psychiatry 2000 Jun;157(6):867-76
Dieperink E, Willenbring M, Ho SB

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OBJECTIVE:

Neuropsychiatric symptoms are commonly associated with chronic hepatitis C virus infection, its sequelae, and its treatment. In particular, interferon, a primary component of treatment for chronic hepatitis C, has been strongly associated with depressive symptoms. This review summarizes current knowledge about the etiology, course, and treatment of neuropsychiatric problems associated with hepatitis C and interferon alpha (IFN-alpha) treatment.

METHOD:

Studies were identified by computerized searches, and further references were obtained from bibliographies of the reviewed articles.

RESULTS:

Chronic infection with the hepatitis C virus is a common and growing problem, often affecting persons with psychiatric and substance use problems. Although changes in cognition, mood, and personality have been described in association with hepatitis C and with IFN-alpha treatment, there has been little systematic study of these changes. CONCLUSIONS: Psychiatrists should become familiar with the clinical spectrum associated with hepatitis C virus infection as well as the neuropsychiatric symptoms related to hepatitis C and IFN-alpha treatment. More studies are necessary to define the neuropsychiatric syndromes associated with this population and to find possible effective treatments. Furthermore, research is needed so that patients with psychiatric problems are not excluded from effective treatments for this growing medical problem.

PMID: 10831463, UI: 20292734

10. Assessment of utilities and health-related quality of life in patients with chronic liver disease.

Am J Gastroenterol 2001 Feb;96(2):579-83 Related Articles, Books
Younossi ZM, Boparai N, McCormick M, Price LL, Guyatt G

Department of Gastroenterology, The Cleveland Clinic Foundation, Ohio, USA.

OBJECTIVES:

Quantitative measures of the value patients place on the state of their health is crucial to understanding their experience, and to calculate quality-adjusted years of life for economic analyses. Patients' values in chronic liver disease remain unexplored, although experts' estimates of utilities have been examined. Our study tests the validity of a widely used utility measure in chronic liver disease and, if valid, establishes the decrement in health-related quality associated with chronic liver disease.

METHODS:

A total of 120 patients with chronic liver disease participated in the study (age 50 10 yr; men 53%; cirrhosis 51%, chronic viral hepatitis 51%, and chronic cholestatic liver disease 30%). All patients completed three instruments: Health Utility Index Mark 2 (scores 0-1), Short Form-36 (scale scores 0-100), and a disease-specific health-related quality of life instrument (Chronic Liver Disease Questionnaire; scores 1-7).

RESULTS:

We found a moderate to strong correlation between scores on the three measures and that impairment worsened as the severity of disease worsened. Patients without cirrhosis and those with Child's A cirrhosis showed substantial decrement in utilities (0.82 and 0.83, respectively) in the range of patients surviving brain tumor. Those with Child's B and C showed a greater decrement (0.67 and 0.56) that was in the range experienced by patients who survive a stroke (0.67). Utilities assessed by Health Utility Index Mark 2 differed substantially from estimates by "expert."

CONCLUSIONS:

We conclude that utilities should be based on patient reports and that the data from this study can inform economic analyses in studies of patients with chronic liver disease.

PMID: 11232711

11. Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions.

J Clin Oncol 2000 Jun;18(11):2316-26
Trask PC, Esper P, Riba M, Redman B

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The increasing use of interferon (IFN) in treating a variety of disorders including, malignant melanoma and hepatitis C, has resulted in the identification and increasing concern about the psychiatric side effects that can result from treatment. These effects can occur either shortly after beginning IFN therapy or later as a result of continued treatment. Studies have reported the incidence of later side effects, which include symptoms of depression, anxiety, and occasional suicidal ideation, to be from 0% to 70%. Case studies have demonstrated that pharmacologic interventions are beneficial in reducing iatrogenic psychiatric symptoms while allowing patients to maintain IFN therapy. The present article provides an overview of the psychiatric effects of IFN therapy, the proposed mechanisms of these side effects, and case studies that provide mechanistic support. In addition, limitations of the current literature are provided with suggestions for treating physicians and a discussion of possible future research directions.

PMID: 10829053, UI: 20291219

12. UPDATE ON LIVER DISEASE & HEPATITIS: ISSUES & CONTROVERSIES IN 1999

(from HepNet)

Quality of Life Issues in Viral Hepatitis

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Key Learning Objectives

At the end of the session, the participants will be able to describe:

- the data on the effects of chronic hepatitis C on quality of life measures
- the issues which affect quality of life evaluation in these patients

Abstract

Health - related quality of life (HRQOL): Utilization of measurement instruments which attempt to define the characteristics of a health state.

The perception of health in an individual depends on many things including:

- societal perspectives
- interest group perspectives
- individual perspectives

Disease labelling alone affects HRQOL (i.e., being told you have hepatitis C and how you are told affects an individuals subsequent HRQOL).

HRQOL: General

a) Descriptive:

- Broadly describes the different dimensions of living with a disease.
- Attempts to use questionnaires to determine HRQOL in a given patient. In
- hepatitis patient studies, SF-36 most commonly used.
- Benefits: validated, access how patient perceives their disease.
- Problems: subjective, potential for manipulation.

b) Utility Assessment:

- tries to determine what it is like to live with a medical condition
- create a summary score or statement

i) Visual Analogue Score:

death ---------- perfect health

ii) Time Trade-off:

"For how many years of perfect health would you trade 10 years of living with your disease as you currently feel?"

iii) Standard Gamble:

"To what extent would you risk death to get rid of your current symptoms?"

Studies of HRQOL in Viral Hepatitis

1) Davis et al, Clin Ther 1994; 16:334

- administered Sickness Impact Profile questionnaire to 160 HCV patients.
- Baseline scores worse in HCV patients than general poulation. IFN treatment improved all scores compared to untreated controls.
- however, responders and non-responders improved to a similar extent.

2) Foster et al, Hepatology 1998;27:209

- SF-36 given to 72 HCV patients, 30 HBV patients and compared to 6,402 healthy
- controls. 50% of HCV former IVDA. Significant reduction in SF-36 scores in all
- health areas in HCV patients.
- HBV patients no different than controls
- SF-36 scores worse in HCV patients with history of IVDA
- SF-36 scores in HCV patients did not correlate with presence of presenting
- symptoms, degree of hepatic inflammation or fibrosis, or ALT level.

3) Bonkovsky and Woolley, Hepatology 1999;29:264

- 642 HCV patients given SF-36 at baseline and 24 wks after IFN therapy finished
- compared to healthy controls (n=750). Baseline scores significantly lower in HCV patients in all categories

- most significant in physical vs mental/emotional

- similar in cirrhotics and non-cirrhotics
- IFN SVR's greater improvement in SF-36 scores than non-SVR's (However -patients not blinded to ALT levels during treatment).

4) Coughlan et al, Gastroenterology 1998;114:A1228

- 93 Irish women - 57 HCV TNA +ve and 36 HCV RNA -ve (persistently).
- Administered General Health questionnaire, HAD and SF-36
- high level of psychological distress in both groups (poor physical and social
- functioning and low vitality/energy)
- essentially no difference between viremic and non-viremic women

HRQOL in Viral Hepatitis:

Summary

1.Reduced HRQOL in HCV patients but not in HBV patients

- In HCV group most significant decrease in former IVDA group
- Decrease in HRQOL in HCV patients does not appear to correlate with degree of hepatic inflammation or fibrosis, ALT level or presence of viremia

Ongoing Issues

- Better assessment techniques needed
- Role of mode of HCV acquisition
- Patients in trials vs unselected
- Comparisons with healthy vs. normal control populations
- Association with co-morbid conditions (eg. anxiety, depression)
- Response to treatment
- Role of disease labelling

13. Quality of Life Impaired in Chronic HCV Infection

Blair CS, Haydon GH, Cossar JA, Miller R, O'Carroll RE, Hayes PL. Quality of the life in chronic hepatitis C infection. J Hepatol 1997;26(suppl 1):224. Abstract C01/88

Blair and colleagues (University of Edinburgh, Scotland) compared the quality of life in 63 HCV-infected patients to that of healthy controls using four standard instruments (Hospital Anxiety and Depression Scale [HAD], Bentall Inventory [measuring fati e], SF-36 scale, and WHO-QOL scale). Controls were matched for age and level of education achieved. The investigators found that HCV-infected patients had significantly higher (ie, worse) scores in all domains of the SF-36 scale: physical role, * physic function, † emotional role, * mental health, * bodily pain, † social function, * vitality,* and general health* (*P<.0001;†P=.0014). Using the WHO-QOL scale, patients also had significantly higher scores in all domains; psychological domain, * physical omain, † environment, * level of independence, † social relationships, * spirituality, * and overall function† (*P<.05; † P<.0001). All HCV-infected patients had HAD scores within the normal range, and Bentall scores did not differ significantly from th e of healthy controls. In addition, there was no significant difference in scores when stratified by route of infection transmission or presence of cirrhosis. This preliminary analysis indicated that patients with HCV infection have an impaired quality life compared with healthy controls. Further, this impaired quality of life apparently is not secondary to anxiety or depression.

14. Hepatitis C and Cognitive Function

Assessment of Fatigue and Psychologic Disturbances in Patients with Hepatitis C Virus Infection
http://www.natap.org/2001/jul/assessment070901.htm

JOURNAL OF CLINICAL GASTROENTEROLOGY 2001;32:413-417
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Abstract

Background: It is a common clinical impression that fatigue is a frequent, and often debilitating, symptom in patients with chronic hepatitis C virus (HCV) infection. However, despite its obvious clinical importance, several aspects of fatigue, including its relationship with the underlying liver disease and the presence of psychologic disturbances, have not been well examined.

Goals: The current study was carried out to assess these issues.

Study: A total of 149 subjects were included in the study and were assigned to one of the following study groups: healthy controls (31), chronic HCV infection (24), combined HCV infection and chronic alcohol abuse (32), alcoholic liver disease (22), and chronic non-liver diseases (40). All subjects were administered investigator-assisted questionnaires designed to analyze the presence and severity of fatigue and psychologic abnormalities.

Results: The mean (±SD) fatigue scores in patients with chronic HCV infection (140 ± 22.9; $p = 0.002$), alcoholic liver disease (127 ± 31.4; $p < 0.001$), mixed (HCV/alcoholic) liver disease (131 ± 29.0; $p < 0.001$), and chronic non-liver diseases (128 ± 35.9; $p = 0.004$) were significantly greater compared to with healthy subjects (101 ± 31.8). The total fatigue scores were higher in HCV-infected subjects compared with the other patient groups, but the differences failed to reach statistical significance. Moreover, the fatigue experienced by patients with HCV did not improve with rest as effectively as in the other study groups. All patient groups had higher scores for psychologic disturbances compared with healthy subjects.

Conclusions: The current study shows that fatigue and psychologic disturbances occur frequently in chronic diseases. The fatigue experienced by patients with HCV infection is more severe and intransigent and responds poorly to relieving factors. Moreover, patients with HCV infection are more depressed and harbour greater feelings of anger and hostility compared with those with non-liver chronic diseases. These observations are important because proper management of the psychologic symptoms may have a favourable impact on the quality of life of patients with HCV infection.

HEPATOLOGY 2002;35:433-439.

Abstract: Patients with chronic hepatitis C virus (HCV) infection frequently report fatigue, lassitude, depression, and a perceived inability to function effectively. Several studies have shown that patients exhibit low quality-of-life scores that are independent of disease severity. We therefore considered whether HCV infection has a direct effect on the central nervous system, resulting in cognitive and cerebral metabolite abnormalities. Twenty-seven viremic patients (HCV+) with biopsy-proven mild hepatitis due to HCV and 16 patients with cleared HCV were tested with a computer-based cognitive assessment battery and also completed depression, fatigue, and quality-of-life questionnaires. The HCV-infected patients were impaired on more cognitive tasks than the HCV-cleared group (mean [SD]: HCV-infected, 2.15 [1.56]; HCV-cleared, 1.06 [1.24]; P = .02). A factor analysis showed impairments in power of concentration and speed of working memory, independent of a history of intravenous drug usage (IVDU), depression, fatigue, or symptom severity. A subgroup of 17 HCV-infected patients also underwent cerebral proton magnetic resonance spectroscopy (1H MRS). The choline/creatine ratio was elevated in the basal ganglia and white matter in this group. Patients who were impaired on 2 or more tasks in the battery had a higher mean choline/creatine ratio compared with the unimpaired patients. In conclusion, these preliminary results demonstrate cognitive impairment that is unaccounted for by depression, fatigue, or a history of IVDU in patients with histologically mild HCV infection. The findings on MRS suggest that a biological cause underlies this abnormality. (HEPATOLOGY 2002;35:433-439.)

HCV and Brain Dysfunction

NATAP - DDW Liver Conference, San Diego, May 21-24, 2001 - Report 11
(thanks to Jules Levin from NATAP)

We know that HIV enters the brain shortly after a person is infected with HIV. It does appear as though individuals with HIV may experience symptoms related to this such as reduced alertness or a slower thinking capacity due to HIV. At both recent liver conferences--DDW and EASL--two different research groups reported research findings suggesting that HCV in individuals with less advanced disease (non-cirrhotics or mild fibrosis) affects the brain and reduces its functioning capacity. This suggests to me that a person with both HCV and HIV may be affected even more with regards to brain functioning. Over the years people with HIV have complained about experiencing fatigue and/or itching. We now know that many people with HIV also have HCV, and that HCV can cause itching and fatigue. The findings reported at DDW and EASL suggest that HCV related fatigue may be associated with the affect of HCV on the brain.

It's known that individuals with advanced cirrhosis can experience hepatic encephalopathy which can cause brain disorder, but it's important to bear in mind that the participants in the studies discussed below did not have such advanced HCV disease so the brain dysfunctioning found was not due to hepatic encephalopathy.

At DDW, Ludwig Kramer and a research group from the University of Austria, reported that "cognitive processing was subclinically impaired in patients as compared to healthy subjects". They studied the impact of HCV infection on sensitive markers of cognitive brain function. Fifty-eight noncirrhotic patients with chronic HCV infection (age, 45Â±13 years, meanÂ±SD) were studied by P300 event-related potentials (an objective measure of cognitive processing) and by the SF-36 questionnaire for assessment of health-related quality of life. Findings were compared to 58 matched healthy subjects. He found that P300 test results were impaired in patients with HCV compared to healthy volunteers, and concluded that patients with chronic HCV infection in the absence of cirrhosis exhibit a subclinical neurophysiological impairment. Cerebral function, however, seems to normalize with antiviral treatment. Although it was not apparent to me if normalization was tied with significant reductions in HCV viral levels, my feeling is that improvements in cerebral function can improve with HCV treatment despite no HCV viral level reductions. More detailed data and discussion are available below at the end of this report.

At EASL, DM Horton presented an oral talk on brain dysfunction in people with HCV for a UK research group from the Imperial College School of Medicine and St Mary's Hospital in London. First he reviewed two studies. He mentioned a UK study (Foster et al 1998) using the SF-36 questionnaire, and reported people with HCV compared to normal controls scored worse in physical and social functioning, energy and fatigue, and other measures. These results were independent of intravenous drug use. In a large US (Johnson et al 1998), 309 IVDUs both with or without HCV were tested for depression and those with HCV (57.2%) were found to have significantly more depressive symptomatology than those who were negative to hepatitis (48.2%).
In an attempt to further define this neuropsychological syndrome, they administered a battery of neuropsychometric tests to 15 patients with histologically mild hepatitis C from liver biopsy. They tested for attention (included: simple reaction time, choice reaction time), working memory (numeric & spatial working memory), and secondary memory (delayed word recall). They found that patients with mild or minimal hepatitis C from liver biopsy were slower in tests of working memory. He noted that although they were slow their accuracy on these tasks was preserved, and this has been described in chronic fatigue syndrome. There were no attention or secondary memory abnormalities.

In the view of these findings they asked themselves if HCV infects cells in the CNS (central nervous system), does this cause cerebral metabolite abnormalities, and is cerebral HCV infection the cause of the observed neuropsychological symptoms? They carried out a proton cerebral magnetic resonance spectroscopy study to determine if metabolite abnormalities exist in the brain of patients with histologically mild hepatitis C. They randomly selected 30 patients with biopsy proven mild or minimal hepatitis due to HCV. As well, they studied 29 matched controls, and 12 eAG+ve patients with chronic HBV. No patient in the HBV or HCV groups had significant fibrosis or cirrhosis. The researchers reported seeing metabolic abnormalities in the testing in those with HCV compared to both normals (volunteers) and chronic HBV patients. There were no statistical differences between the normals and those with HBV. These abnormalities were not due to hepatic encephalopathy. They described the abnormalities as being similar to those abnormalities observed in HIV. Again, no patient in this study had significant fibrosis or cirrhosis. None of the study participants had used IV drugs in the 6 months preceding

the study. There was no statistical difference in the study results between those with or without prior drug use. Those with prior drug use had the same abnormalities as those who never used IV drugs. The researchers concluded that prior drug use did not affect the outcome of the study.

Is there direct infection by HCV of the CNS?

He presented a suggested potential model by which this could happen. Microglial cells in the brain turn over slowly and are replenished by circulating monocytes, possibly up to 30% in one year. Circulating monocytes are potentially infectable by HCV, and may carry the virus across the blood brain barrier into the brain and the microglial cells. Once in the cells they become activated and produce chemokines, cytokines, and neurosteroids which may mediate the neuropsychiatric symptoms described in this presentation. The question still remains--does HCV infect the microglial cells in the brain? The only way to answer this question is to conduct direct post mortem viralogic examination of brain tissue which is being currently undertaken at Imperial College School of Medicine in London.

He also suggested that of equal or possibly greater importance is the possibility that the brain may act as a sanctuary site for HCV allowing immune evasion and protection against antiviral therapy. He suggested that cessation of viral production from the liver may occur during phase 1 of viral decline after starting HCV therapy, but the slower viral decline during phase 2 may be due to a continued release of virus from the brain. He suggested that an alternative explanation for possible brain dysfunction seen with HCV could be that systemic cytokines cross the blood-brain barrier and may exert an effect. But he discounted this theory because in this study patients with HBV had normal spectroscopy. HCV antiviral therapy has been administered to the study patients and results are pending. In the study reported at DDW, and discussed above, the study authors reported therapy improved cerebral function, and they suggest their data may indicate a direct action of HCV infection on the brain.

DDW Abstract:

COGNITIVE BRAIN FUNCTION IS SUBCLINICALLY IMPAIRED IN PATIENTS WITH CHRONIC HEPATITIS C - DOES HEPATITIS C AFFECT THE BRAIN?

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Fatigue and depression occur more frequently in chronic hepatitis C virus (HCV) infection than in other causes of chronic liver disease. However there is no correlation between severity of hepatitis and cerebral symptoms. It has been hypothesized that HCV exerted a direct effect on the brain. We studied the impact of HCV infection on sensitive markers of cognitive brain function. Fifty-eight noncirrhotic patients with chronic HCV infection (age, 45Â±13 years, meanÂ±SD) were studied by P300 event-related potentials (an objective measure of cognitive processing) and by the SF-36 questionnaire for assessment of health-related quality of life. P300 latency is related to signal-processing speed; P300 amplitude reflects the amount of conscious attention paid to a stimulus. Findings were compared to 58 matched healthy subjects. We found

that cognitive processing was subclinically impaired in patients (P300 latency: 361Â±38 ms, meansÂ±SD) as compared to healthy subjects (344Â±27 ms, p=0.01). Similarly, P300 amplitude was reduced in patients with HCV infection (12Â±7 vs. 18Â±7 ÂµV, p<0.01). Health-related quality of life was significantly reduced in patients with HCV infection but there was no clear correlation between neurophysiological function and health-related quality of life or activity of hepatitis. In 7 out of 9 patients who were followed during antiviral combination treatment, P300 latency was improved after 12 weeks (345Â±29 ms) as compared to baseline (363Â±48 ms, p=0.08). In conclusion, patients with chronic HCV infection in the absence of cirrhosis exhibit a subclinical neurophysiological impairment. Cerebral function, however, seems to normalize with antiviral treatment. Our data might indicate a direct action of HCV infection on the brain. A theory that I've heard is that improvement from therapy is due to ribavirin because interferon does not enter the brain. But in HIV it's hypothesized that brain or cognitive functioning may improve also because of improved immune function and not necessarily due only to direct antiviral drug affect in the brain or CNS.

Legal Aid Offices in British Columbia

This is a list of the offices in British Columbia that can take applications for legal aid. Call the office nearest you for more information and office hours.

Abbotsford	(604) 859-2755
Alert Bay	(250) 974-5046
Burnaby	(604) 451-8944
Burns Lake	(250) 692-7534
Campbell River	(250) 287-9521
Chetwynd	(250) 788-3113
Chilliwack	(604) 795-2275
Courtenay	(250) 897-1400
Cranbrook	(250) 489-3375
Dawson Creek	(250) 782-7366
Duncan	(250) 715-1855
Fernie	(250) 423-9241
Fort Nelson	(250) 774-6707
Fort St. James	(250) 996-7700
Fort St. John	(250) 785-1788 and (250) 785-6509
Golden	(250) 344-5258
Grand Forks	(250) 442-8360
Hazelton	(250) 842-5218
Invermere	(250) 342-4447
Kamloops	(250) 314-1900
Kaslo	(250) 353-2292
Kelowna	(250) 763-8613
Ladysmith	(250) 245-7141
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Lilloet	(250) 256-0094
Lytton	(250) 455-6637
Maple Ridge /Pitt Meadows	(604) 467-3011
Masset	(250) 626-3925
Merritt	(250) 378-6112
Nanaimo	(250) 741-0242
Nelson	(250) 352-3147
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New Westminster	(604) 524-0381
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Parksville	(250) 954-0140
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Port Alberni	(250) 724-5137 and 723-8281
Port Coquitlam	(604) 944-8841
Port Hardy	(250) 949-8333
Powell River	(604) 485-9871
Prince George	(250) 564-9717 and 562-3591
Prince Rupert	(250) 627-1364
Quesnel	(250) 992-8391
Revelstoke	(250) 837-5196
Richmond	(604) 273-9311
Salmon Arm	(250) 832-5050
Sechelt	(604) 885-5509
Skidegate	(250) 559-8811
Smithers	(250) 847-1595
Squamish	(604) 892-5114
Surrey	(604) 585-6595
Terrace	(250) 635-2133
Ucluelet	(250) 726-4307
Vancouver	(604) 601-6300
Vancouver Aboriginal Law Centre	(604) 601-6440
Vernon	(250) 545-3666
Victoria	(250) 388-4516
Williams Lake	(250) 392-2941
Prisoners*	(604) 853-8712

***Prisoners Legal Services is for inmates in the Abbotsford area.**

Legal Services Society also provides information on its Web site about legal aid and about many of its booklets and brochures on different aspects of the law. The LSS Web site address is: *www.vcn.bc.ca/lssbc/*