

a series of fact sheets written
by experts in the field of liver
disease

An Overview of Extrahepatic Manifestations of Hepatitis C

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THE HEPATITIS C VIRUS MAINLY AFFECTS THE LIVER, but there are many other conditions that are associated with hepatitis C. Extrahepatic manifestation means diseases or conditions that affect organs other than the liver. Extrahepatic manifestations of hepatitis C can be found in the skin, eyes, joints, immune system, nervous system and kidneys. Some of these conditions – cryoglobulinemia, for example – are somewhat more common and well-documented, while others are infrequent or their association with hepatitis C has not yet been proven.

Several studies have found that between 70-74% of HCV patients experience extrahepatic manifestations. Some of the most common symptoms and conditions reported include fatigue, arthralgias (joint pain), paresthesias (feeling of numbness and tingling), myalgias (muscle pain), pruritus (severe itching), sicca syndrome (dryness of the mouth and eyes), insulin resistance, type II diabetes, kidney disease, thyroid disease and many other conditions. Many of the conditions have in some way been related to cryoglobulin (an abnormal blood protein) production.

It is important to remember that the vast majority of people with hepatitis C may never experience the more severe types of these extrahepatic manifestations. However, if you believe that you may have any of these conditions talk to your medical provider for more information and diagnosis. If possible have your regular provider refer you to a provider who specializes in these types of conditions.

Arthralgia is a common symptom of hepatitis C that is characterized as joint pain, but without inflammation of the joints that is associated with arthritis.

Arthritis is a condition characterized as inflammation of the joints. Hepatitis C-related arthritis (HCVrA) is estimated to affect about 4% of the HCV population, but since most patients will not see an arthritis specialist the true number is likely higher. Hepatitis C-related arthritis is classified into two groups – polyarthritis and mono-oligoarthritis. Polyarthritis is similar to rheumatoid arthritis but is less serious. Mono-oligoarthritis affects the medium and large-sized joints – typically the ankles.

Behcet's Disease is a disease that presents as ulcerations in the eyes, mouth and genitals but can also affect any organ of the body and is caused by coagulation and destruction of arteries and veins.

Canities is a condition believed to be associated with hepatitis C that causes premature graying of the hair, but is uncommon in people with hepatitis C.

Cerebral Vasculitis is a disorder that is characterized by inflammation and cell death of arteries in the brain. The cause of cerebral vasculitis is unknown, but it is thought to be caused by immune dysfunction.

Cryoglobulinemia is one of the most common disorders associated with hepatitis C. Cryoglobulinemia is a blood disorder caused by abnormal proteins in the blood called cryoglobulins that precipitate or clump together when blood is chilled and dissolve when warmed. These proteins can be deposited in the small and medium sized blood vessels, which restricts blood flow and can lead

to further problems. There is a blood test used to detect cryoglobulinemia, but it is important that the blood sample is kept at room temperature and handled carefully. Even though the markers for cryoglobulinemia are common in people infected with hepatitis C, most people with hepatitis C are not symptomatic, but those who are symptomatic can have mild, moderate or severe illness. Symptoms of cryoglobulinemia include red or purple blotching skin, and joint and generalized pain. Cryoglobulinemia can affect the skin, kidneys, nerves and joints. Conditions associated with cryoglobulinemia include vasculitis (inflammation of the blood vessels), peripheral neuropathy, Reynaud's Phenomenon (hands that are sensitive to cold temperature and turn white, red, blue), and Non-Hodgkin's lymphoma (a collection of diseases). Treating cryoglobulinemia consists of treatment of the underlying disease (hepatitis C) as well as the administration of medications to suppress the immune system, and plasmapheresis (blood is taken from the body, filtered and returned to the body).

Diabetes is a disorder caused when the body is unable to process sugars. Diabetes that is seen in people with hepatitis C is type 2 diabetes which is a slowly progressive disease. A direct link between type 2 diabetes and hepatitis C has not been clearly established; but it is found more commonly in people with hepatitis C than in the general population.

Fatigue is one of the most common symptoms of hepatitis C and can range from mild to moderate to severe. It is thought that the fatigue is caused by the body's immune response to hepatitis C and as well as by direct affect of the virus on the body.

Fibromyalgia is a disorder characterized by aches, pain, stiffness, soft tissue tenderness, general fatigue and sleep disturbances. Pain is the most common symptom of fibromyalgia and it is usually confined to muscles and ligaments. Although fibromyalgia has not been linked to hepatitis C, it is a condition that is more commonly found in people with hepatitis C than in the general population. A comprehensive approach with many different healthcare providers

(including the person suffering from Fibro) is the best strategy.

Hypertrophic Cardiomyopathy (HCM) is a form of a disease of the heart where enlargement and thickening develops in one part of the heart. Very rarely has it been associated with hepatitis C.

Immune Thrombocytopenic Purpura (ITP) is an autoimmune bleeding disorder caused when the blood doesn't clot. Symptoms of ITP are easy bruising of the skin as well as bruising under the skin that can be seen as red or purple dots on the skin. In severe cases bleeding from the nose, gums and gastrointestinal or urinary systems can occur. Increased prevalence of ITP has been found in people with HCV and in those who have been treated with HCV medications.

Insulin Resistance (IR) is a condition caused by the inability of cells to absorb glucose. This leads to the pancreas releasing more insulin so there is an excess amount of both glucose and insulin in the bloodstream. HCV can induce IR. IR lowers treatment response and can speed up HCV disease progression.

Lichen myxoedematosus (LM) is also known as papular mucinosis. LM is a rare chronic condition that has been linked to HIV infection, hepatitis C infection, and exposure to toxic oil and contaminated L-tryptophan. LM is characterized by small papules (bumps) that affect the face, trunk and extremities that can progress on to skin tightening and hardening.

Lichen Planus is a skin disorder that is characterized by small elevated bumps or pimples and usually appears on flexor surfaces (the muscle that brings two bones together, causing flexion of the part) – arms, trunk, genitals, nails and scalp. Symptoms can include scaling, itching, hair loss, skin lesions, plaque, and pain.



Hepatitis C-related lichen planus is caused by HCV replication in epithelial (skin) cells. Treatment consists of treating the underlying cause (hepatitis C), but treatment with HCV medications in managing or relieving symptoms of lichen planus has been inconsistent. Cortisone creams/ointments and cortisone injections are also used for managing the symptoms. Avoid substances that can trigger a flare-up of symptoms including alcohol, tobacco, spicy foods, peppermint, cinnamon, citrus type foods and stressful situations.

Lung Abnormalities and diseases can be triggered by hepatitis C. **Idiopathic pulmonary fibrosis** is defined as scarring of the lungs. **Chronic Obstructive Pulmonary Disease (COPD)** involves two diseases – chronic bronchitis and emphysema. **Asthma** is a chronic disease that inflames and narrows the airways. **Hypoxemia** is a condition in which there is an abnormally low amount of oxygen in the blood due to the inability of the lungs to perform their chief function of gas exchange. Interferon can also cause various lung abnormalities.

Membranoproliferative Glomerulonephritis (MPGN) is a condition affecting the kidneys that is usually (but not always) associated with cryoglobulinemia. Symptoms include weakness, edema and arterial hypertension. Treatment consists of treating the underlying disease (hepatitis C). However, if there is severe kidney impairment, ribavirin should be avoided.

Membranous Nephropathy is a disease of the kidneys that is associated with hepatitis C but not with cryoglobulinemia. It is believed that circulating HCV antibodies and viral particles are deposited in the kidneys causing damage. Treatment consists of interferon plus ribavirin. If there is severe kidney damage then the use of ribavirin should be avoided.

Mooren Corneal Ulceration is associated with hepatitis C and can cause pain, inflammation, tearing and loss of sight.

Multiple Myeloma is a form of cancer of the plasma

cells in the bone marrow that causes excessive growth of the plasma cells. This interferes with the production of red and white blood cells and platelets, and can cause anemia, infections, and bleeding.

Neutropenia is defined as an abnormally low white blood cell (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) count. Decreased production of white blood cells can lead to increased risk for infections. Interferon can also cause neutropenia.

Non-Hodgkin's Lymphomas (NHL) are cancers of lymphoid tissues. NHL can be low-grade (slow growing) or high-grade (rapidly growing) cancer. NHL is uncommon, but the incidence of NHL is higher in people with hepatitis C than in the general population. Studies have found that successful treatment with interferon and ribavirin can lead to remission of NHL.

Paresthesia is a sensation of tingling, pricking, or numbness of skin. The exact cause of HCV-related paresthesia is unknown but it has been linked to other conditions found in people with hepatitis C such as fibromyalgia, peripheral neuropathy and hypothyroidism.

Peripheral Neuropathy (PN) is characterized by numbness, burning, pins and needles sensations, crawling skin, and itching that occurs most often in the hands and feet, but can appear in other areas of the body. People with HCV-related PN should be tested for Cryoglobulinemia. In one study, it was found that 15.3% of people with HCV were diagnosed with PN. Treatment consists of treating the underlying disease (HCV) and avoiding any medications that cause or that can make neuropathy worse. It is also advised that patients should avoid or reduce alcohol consumption.

Porphyria Cutanea Tarda (PCT) is a skin disorder caused by the reduced activity of an enzyme resulting in an overproduction of and build up of the protein uroporphyrinogen in the blood and urine of patients, and hepatitis C has been suggested as a cause. Other causes include hereditary hemochromatosis



Porphyria Cutanea tarda

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(accumulation of iron in the liver), heavy alcohol use and estrogens. Characteristics of PCT develop in areas that are exposed to the sun with resulting skin lesions (blisters) on the hands, forearms, back of the neck and face. PCT can also cause skin discoloration, either darkening or lightening of the skin, increased facial hair, thickening of the skin, and alopecia (hair loss). Treatment of PCT can involve phlebotomy, dietary iron restriction, reducing alcohol consumption, avoiding exposure to the sun or the use of sunscreen, and avoiding or minimizing estrogen exposure.

Pruritus is one of the most common symptoms reported by people with hepatitis C (15%), but is more commonly found in people with end stage liver disease. Pruritus is itching that may be localized to a specific part of the body such as hands and feet, but it can also be a generalized itching all over the body. It can be related to high bilirubin levels, autoimmune disease or dry skin, and can be a side effect of treatment. Use of moisturizing lotions, oatmeal baths or lotions, antihistamines, and cortisone creams and opiate drugs can help.

Raynaud's Syndrome is a disorder that causes the blood vessels in the fingers, toes, ears, and nose to constrict or narrow. Treatment consists of managing the condition since there is no cure for Raynaud's.



Raynaud's of the fingers

Mayo Clinic

Sialadenitis is an inflammatory disease that causes dry mouth and eyes and is associated with hepatitis C infection. Sialadenitis destroys the salivary glands.

Sjogren's Syndrome (SS) is an autoimmune disease that affects the eyes and mouth, making them dry. Although hepatitis C has not been directly linked to SS, it is found more often in people with hepatitis C than in the general population. There is no cure for SS. Treatment consists of managing or lessening the symptoms.

Spider Nevi is characterized by the appearance on the skin of small red dots with radiating lines resembling a spider web. Spider nevi can be found anywhere on the body but usually affects the face and trunk.



Spider Nevi (spider angioma on the cheek)

Logical Images

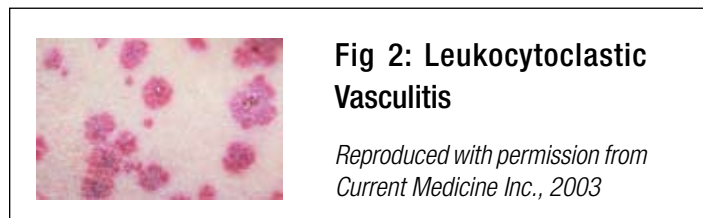
Systemic Lupus Erythematosus (SLE) is an autoimmune disease. The exact cause of SLE is unknown, but it is thought that the immune system mistakenly recognizes proteins in the blood as foreign invaders and destroys normal proteins. Symptoms vary widely from patient to patient as do episodic attacks or flare-ups. The disease usually attacks one organ, but over time other organs can be affected and after many years SLE can lead to death. There are many strategies for managing SLE including the use of NSAIDs, acetaminophen, corticosteroids, immunomodulating drugs, and anticoagulants.

Thrombocytopenia is generally defined as a platelet count below 100,000 to 150,000 cells per microliter of blood. The normal range of platelets is between 150,000 and 450,000 cells per microliter of blood. Most studies have found a correlation between the stage of fibrosis and thrombocytopenia in HCV patients. Platelets are proteins that help the blood clot. Treatment with interferon can also cause thrombocytopenia.

Thyroid Disease can be caused by many factors including hyperthyroidism (too much thyroid hormone) and hypothyroidism (too little thyroid hormone) released by the thyroid gland. The direct link between hepatitis C and thyroid disease (usually hypothyroidism) is unclear, but thyroid disease is more commonly seen in people

with hepatitis C than in the general population. HCV treatment can also induce thyroid disease, but thyroid function will return to normal for about 95% of people who develop treatment-related hypothyroidism when treatment is stopped.

Vasculitis (essential cryoglobulinemic vasculitis) is the inflammation of blood and lymphatic vessels and is caused by cryoglobulins – antibodies that precipitate (clump together) under cold conditions and dissolve on rewarming. Vasculitis is associated with hepatitis C-related cryoglobulinemia (see *cryoglobulinemia* above). Symptoms include purpura (discoloration of the skin caused by bleeding vessels) petechiae, (red pin point rash caused by minor hemorrhaging), and usually affects the lower extremities of the body. Other symptoms include fever, itching welts, muscle ache and pain and enlarged lymph nodes as well as peripheral neuropathy. Treatment consists of treating the underlying cause (HCV) with interferon plus ribavirin, but has shown mixed results. Vasculitis can also affect other organs such as the kidneys, liver, lungs, heart and central nervous system, but this is uncommon. A skin biopsy will show inflammation of the small blood vessels.



Vitiligo is a condition in which there is loss of pigmentation – usually around the mouth, eyes, nose, elbows, knees and wrists.

Waldenstrom Macroglobulinemia (WM) is a chronic low-grade type of cancer of the lymph cells. Treatment of WM depends on the degree of disease progression.

Be Sure to Check Out All of the Factsheets in This Series: Extrahepatic Manifestations of HCV

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- Cryoglobulinemia
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- Sjögren’s (Show grins) Syndrome
- Systemic Lupus Erythematosus
- Vitiligo
- Waldenstrom Macroglobulinemia

For more information about hepatitis C, hepatitis B and HCV coinfections, please visit www.hcvadvocate.org.

• *hcsPFACTsheet* •
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