How is PSC Diagnosed?

By David Rhodes

Increasingly, PSC is diagnosed in otherwise asymptomatic patients by observing elevated serum liver enzyme levels in routine blood tests (liver function tests). Serum liver enzyme levels elevated in PSC include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyltranspeptidase (GGT). Elevated ALT and AST generally indicate liver cell damage; these enzymes are formed mainly in the liver, and their release to the blood implies liver damage. Elevated serum ALP is usually indicative of a cholestatic liver disease or bile-duct blockage. However, because this enzyme can also be elevated in bone disease and during normal bone growth in teenagers, a GGT test is often performed to verify liver involvement. Once a cholestatic liver disease is suspected, antibody tests are typically performed to rule out various viral diseases (such as viral hepatitis), and to attempt to distinguish amongst the various types of autoimmune cholestatic liver diseases. Primary biliary cirrhosis (PBC) is strongly suspected when a patient is positive for anti-mitochondrial antibodies. Autoimmune hepatitis is suspected when patients are positive for smooth-muscle and/or anti-nuclear antibodies or antibodies to liver/kidney microsome type 1. Patients with primary sclerosing cholangitis (PSC) generally do not exhibit a clearly defined set of autoantibodies. Autoimmune hepatitis is suspected when patients are positive for smooth-muscle and/or anti-nuclear antibodies or antibodies to liver/kidney microsome type 1. Patients with primary sclerosing cholangitis (PSC) generally do not exhibit a clearly defined set of autoantibodies. Anti-cardiolipins are the single group of antibodies that have been shown to have a significant correlation with the severity of PSC.

If other causes of cholestatic liver disease are ruled out, endoscopic retrograde cholangiopancreatography (ERCP) would typically be performed to visualize the biliary tree and to look for the characteristic strictures and beaded appearance of the bile-ducts associated with PSC. MRCP (magnetic resonance cholangiopancreatography) is being increasingly used for diagnosis of PSC, although ERCP remains the gold standard. A liver biopsy might then be performed for histological staging of the disease. PSC would be immediately suspected in patients presenting with inflammatory bowel disease (IBD) and elevated ALT, AST and ALP, because over 75% of PSC patients also have IBD. Typical early symptoms of PSC include: fatigue, pruritus (itching), and jaundice associated with elevated serum bilirubin.
Experimental Therapy: Fibrates

By David Rhodes

In Japan, researchers have been experimenting with a class of drugs called fibrates for cholestatic liver diseases (Dhomen et al., 2004; Itakura et al., 2004; Kanda et al., 2003; Kita et al., 2002; Nakai et al., 2000; Ohira et al., 2002). Fibrates are lipid-lowering agents that are activators (agonists) of the nuclear receptor transcription factor, peroxisome proliferator-activated receptor alpha (PPARα). The binding of fibrates to PPARα alters the expression of a number of genes involved in lipid metabolism and bile acid synthesis and transport (Fruchart et al., 1999; Hunt et al., 2000). Fibrates reduce plasma triglyceride levels, increase lipoprotein lipase synthesis, and favorably alter apolipoprotein and serum cholesterol levels (Fruchart et al., 1999). Moreover, fibrates are potent anti-inflammatory molecules through an indirect modulation of the nuclear factor-kappa B activity (Fruchart et al., 1999). Thus, fibrates inhibit atherosclerotic development not only by improving the plasma lipid profile but also by reducing inflammation in the vascular wall (Fruchart et al., 1999; Hunt et al., 2000). In both primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), fibrate treatment tends to lower serum alkaline phosphatase (ALP) and gamma-glutamyltranspeptidase (GGT) levels (Dhomen et al., 2004; Itakura et al., 2004; Kanda et al., 2003; Kita et al., 2002; Nakai et al., 2000; Ohira et al., 2002). These enzyme levels are typically elevated in cholestatic disease. It is thought that the reductions in serum ALP and GGT may be in part due to an effect of fibrates on bile transport; specifically the induction (via PPARα) of the multidrug resistance protein (MDR3) (also known as PGP3 or Multidrug Resistance 3). This protein is encoded by the ABCB4 gene (gene map locus 7q21.1), and is thought to be an ATP-dependent "flipase" that moves phospholipids from the inner to the outer leaflet of the canalicular membrane (Kok et al., 2003). The favorable effects of fibrates on ALP and GGT may also be related to alterations on bile acid synthesis, and bile acid conjugation, and sodium-dependent bile salt transporter expression (Barbier et al., 2003; Jung et al., 2002; Roglans et al., 2004).

The mouse equivalent of the human MDR3 protein is Mdr2, encoded by the gene Abcb4. You may recall that in our first newsletter (Vol. 1, Issue 1, Jan 2005) it was noted that mice deficient in Mdr2 (mdr2(-/-)) develop sclerosing cholangitis by a multistep process involving regurgitation of bile from leaky ducts into the portal tracts. This leads to induction of periductal inflammation, followed by activation of periductal fibrogenesis, finally causing oblitative cholangitis owing to atrophy and death of bile duct epithelial cells (Fickert et al., 2004). Fibrates induce Mdr2 expression in mice (Kok et al., 2003). Shoda et al. (2004) have suggested that the decreased function of ATP binding cassette protein B4 (ABCB4), which is rate-limiting for biliary phospholipid secretion, predisposes individuals to cholestasis and/or cholangitis. They show that bezafibrate may enhance the capacity of human hepatocytes to direct phospholipids into bile canaliculi via redistribution of ABCB4 to the canalicular membrane. They suggest that this provides a rationale for the use of bezafibrate to improve cholestasis and/or cholangitis due to impaired function of ABCB4 (Shoda et al., 2004).

Bezafibrate and fenofibrate are now being considered as experimental drugs (in combination with ursodeoxycholic acid) in PBC patients in Europe and the U.S.A. (Bergasa et al., 2004). It would seem reasonable to explore whether this class of drugs is also of benefit in PSC. Because fibrates modify the expression of key factors involved in bile-acid synthesis and biliary-lipid secretion in gallstone patients (Roglans et al., 2004), and it is well known that gallbladder disease and hypercholesterolemia are commonly associated with PSC, it would seem logical to at least assess the beneficial effects of fibrates on these conditions associated with PSC.

References


For additional references on fibrates, please see: http://www.psc-literature.org/fibrate.htm
The Birth and Growth of a Foundation

On January 4, 2005, a foundation was born and named PSC Partners Seeking a Cure. As any parent knows, while labor and birth may be difficult, the true work lies ahead in nurturing growth. The celebration of our birth is over and our next celebration will be our first birthday, when we will reflect upon our first year. Now is the time for all of us to share in the growth of our foundation so that we have much to celebrate next year.

Fundraising will be a big topic at our first conference this April. Supporting patient education, organ donation, and medical research requires a large bank account. What seems an insurmountable task at first becomes less so when you break it down one country at a time, one state at a time, one town at a time, one person at a time. Together we can not only set high goals, but we can reach them.

Right now we have a business size donor card that can be handed or mailed to family and friends, neighbors and coworkers. You can get these by contacting me at ldbria@comcast.net. Eleven members are already on board, handing out these cards to their friends, family members, and colleagues.

We have bracelets on the way that we can all sell not only to our friends and family, but also through local groups such as high school Key Clubs, Rotary groups, Lions Clubs and even the Boy Scouts and Girl Scouts. Think about where you have a personal contact and then ask if they might help you to sell some bracelets. These can be ordered by contacting or messaging Bill Wise.

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We are looking into MissionFish on e-Bay as a possible future source of donations and we will let you know if this goes forward. Two new fundraising projects are in progress: Nichole Rowland's football game fundraiser with Rick Manning Jr. and other Carolina Panthers, and Joan Kantor's letter writing campaign for corporate sponsors.

We are seeking all your good ideas for fundraising events. If you are coming to the conference, please bring along your ideas and the information that might make them a reality. If you are unable to attend the conference, then please send your ideas to me at ldbria@comcast.net so that I can look into them and get back to you.

We hope to keep moving ahead with new ideas while helping our existing plans to grow. We will celebrate our successes of the first year while looking forward to the next year’s accomplishments. Together we can all watch our baby mature from infant to toddler to adolescent to teen. With the work of our members now and those to come, we can only hope that our foundation makes it to its adult and senior years and maybe even to retirement! Wouldn’t it be great to find a cure?

Lee Bria
What are PBC and PSC, and how do they differ?

By David Rhodes

Both primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic cholestatic liver diseases. Both are presumed to have an autoimmune basis. Both conditions involve progressive destruction of bile ducts leading to chronic cholestasis and biliary cirrhosis. This is often accompanied by complications, such as portal hypertension and liver failure. Both conditions may eventually require liver transplantation. Both diseases may recur following liver transplantation. Both diseases are currently treated in their early stages with ursodeoxycholic acid (UDCA).

PBC involves progressive destruction of the small, interlobular bile ducts. It affects mainly women (female to male ratio of 9:1), with a peak incidence between the ages of 40 and 60 years. PBC patients typically exhibit anti-mitochondrial antibodies directed against 2-oxoacid dehydrogenase complexes in the inner mitochondrial membrane, the most important being the pyruvate dehydrogenase complex.

PSC involves inflammation, fibrosis, and stricturing of the intrahepatic and extra-hepatic biliary tract, with associated ductopenia. About two thirds of the patients are men, with an average age of about 40 years at presentation. Approximately 75% of patients with PSC also have inflammatory bowel disease (IBD), mostly chronic ulcerative colitis (UC), but sometimes Crohn's disease. PSC patients typically exhibit perinuclear anti-neutrophil cytoplasmic antibodies and/or other auto-antibodies. About 6% of PSC patients have a version of PSC called small-duct PSC which may have a more benign course.


Poetry Corner

A Poem from a PSC Care-Giver

This poem is dedicated to all PSC care-givers who are worried about their loved-one's livers.

I first heard of primary sclerosing cholangitis, PSC, in the summer of two-thousand and three,
when my son was diagnosed with this disease, and UC, which stands for ulcerative colitis, a form of IBD.
These two diseases often come together, you see.

Since the dreadful day of diagnosis, following an ERCP (endoscopic retrograde cholangiopancreatography),
I have learned that this disease has poor prognosis,
with bile-duct loss leading to cirrhosis (and eventual hepatic encephalopathy). Moreover,
PSC comes with increased risk of cholangiocarcinoma.
Liver transplantation as a "cure" is surely a misnomer,
for there is evidence that PSC recurs.
To make matters worse,
UC also comes with risk of colon cancer.
Boy, I wish I could find an answer!

Are there genes conferring susceptibility?
Some say they may be in the major histocompatibility complex.
What is the role of autoimmunity?
Why does this disease mostly affect the male sex?
Are the triggers environmental or infectious?
Will ursodeoxycholic acid delay progression,
or even help promote remission?

Some promising results have been obtained with bezafibrate.
Oh, wouldn't it be great
if such medication could improve the bile flow,
and prolong the liver for a while.

Will researchers find a cure
before our son has to endure
the tortuous path to liver failure?
If I find an answer, I'll be sure
to post it on PSC Literature.

David Rhodes (father of Steven, PSC 2003)
**How does Ursodiol Work?**

By David Rhodes

Ursodiol (ursodeoxycholic acid; UDCA; URSO; Actigall) is a bile acid originally identified in black bears; the name ursodiol derives from the Latin name of the bear family, Ursidae (Hagey et al., 1993). It was first used in Western medicine for the dissolution of gallstones in gall bladder disease patients.

Both PBC and PSC cause accumulation of toxic bile acids (such as deoxycholic acid (DCA)) in the liver, leading to cell death. The beneficial effects of ursodiol in PBC and PSC patients are in part attributable to a protective effect of this bile acid against toxic bile acids in liver cells (Paumgartner and Beuers, 2002). In addition, ursodiol increases bile transport activity, stimulating hepatobiliary secretion by preserving activity of the bile-salt export pump (BSEP), a key component of the bile transport system in the liver (Paoloni et al., 2002).

UDCA also seems to have anti-inflammatory properties. It binds to the glucocorticoid receptor and suppresses a key inflammatory component, nuclear factor-kappa B (NFKB) (Miura et al., 2001) [see article on Inflammatory Bowel Disease Genetics (Part 1) in this issue].

Anticholestatic effects of ursodiol have also been reported in other liver diseases, including progressive familial intrahepatic cholestasis, intrahepatic cholestasis of pregnancy, and liver disease associated with cystic fibrosis (Colombo et al., 1992; Angulo, 2002; Paumgartner and Beuers, 2002).

**References**


For additional references on ursodiol please see: [http://www.psc-literature.org/urso.htm](http://www.psc-literature.org/urso.htm)

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**Inflammatory Bowel Disease Genetics (Part 1)**

By David Rhodes

About 75% of patients with primary sclerosing cholangitis (PSC) also have inflammatory bowel disease (IBD); mostly ulcerative colitis (UC), and sometimes Crohn's disease. Because of this relationship between IBD and PSC, it is important to consider the factors that may contribute to IBD as this may provide clues to the causes of PSC. A large number of studies have shown that heritable factors (i.e. genes) are of central importance in determining predisposition to IBD. This article is the first in a series which will discuss the complex genetic basis of IBD.

There has been rapid progress in identifying IBD susceptibility genes in the last few years. The first IBD gene to be identified was the NOD2/CARD15 gene (gene map locus 16q12) associated with Crohn's disease, and so it seems appropriate to begin this article with a discussion of this gene which has been the most intensively investigated.

CARD stands for "Caspase recruitment domain-containing protein". NOD stands for "nucleotide-binding oligomerization domain". The NOD2/CARD15 protein encoded by the

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**Research Review Act**

By Ricky Safer

There is some good news to report for the 75-80% of PSC patients who also are affected by IBD (inflammatory bowel disease). On November 30, 2004, President Bush signed into law the first ever United States legislation aimed at helping people affected by Crohn’s disease and ulcerative colitis. The Crohn’s and Colitis Foundation of America (CCFA) was instrumental in the passage of this law. The Research Review Act provides that:

1. By May 2005, The Center for Disease Control and Prevention must issue their epidemiology study report to Congress, which will document the true prevalence of IBD in the United States and the demographics of this population. Hopefully, this information will help unveil the role of genetic and environmental factors in the development of IBD.

2. The General Accountability Office will issue their report to Congress on Medicare and Medicaid’s coverage standards for various therapies that IBD patients must undergo. Gaps in Medicare/Medicaid coverage will be identified, so that IBD patients can become better educated on how to push for changes in insurance reimbursement policies.

3. The General Accountability Office will also send their report to Congress on the problems that IBD patients experience when they apply for Social Security Disability benefits and also on recommendations for improving the application process.

These three reports will improve the quality of life for people affected by IBD. Thanks are due to President Bush and the members of Congress who helped further our cause.

NOD2/CARD15 gene is thought to be an intracellular receptor for bacterial products that controls signals that lead to activation/inactivation of nuclear factor-kappa B (NFkB). NFkB activation in turn activates tumor necrosis factor alpha (TNFa), which then activates the inflammation response.

Recent studies indicate that the normal NOD2/CARD15 protein senses muramyl dipeptide derived from peptidoglycans of bacterial cell walls. Normally, when activated by muramyl dipeptide, the NOD2/CARD15 protein inhibits the signaling from a receptor, Toll-like receptor 2 (TLR2), to NFkB. But when the NOD2/CARD15 gene is mutated, the NOD2/CARD15 protein is unable to sense muramyl dipeptide and prevent Toll-like receptor 2 from signaling to NFkB. TNFa is therefore switched on, and consequently there is uncontrolled inflammation, resulting in Crohn's disease.

These discoveries are important because they define how a change in the signaling pathway by which bacterial products are sensed in the gut can lead to inflammation. This has provided several clues as to other genes that may regulate inflammation in inflammatory bowel disease.

A recently identified gene determining susceptibility to Crohn's disease is the gene NFKBIA (nuclear factor of kappa light chain gene enhancer in B cells inhibitor, alpha) (gene map locus 14q13). The protein encoded by this gene normally down-regulates the activity of NFkB. Mutation in the NFKBIA gene produces an effect similar to the NOD2/CARD15 mutation; that is, uncontrolled activation of NFkB, uncontrolled TNFa activation, and inflammation. Not surprisingly, certain mutations (polymorphisms) in the TNFa gene (gene map locus 6p21.3) may also contribute to IBD. Moreover, polymorphisms in the promoter region of NFKB1 (the gene encoding NFkB) (gene map locus 4q23-q24) are associated with risk of ulcerative colitis.

While Toll-like receptor 2 (TLR2) senses peptidoglycans of bacterial cell walls, Toll-like receptor 4 (TLR4) senses lipopolysaccharides excreted by Gram-negative bacteria. Like TLR2, TLR4 activation sends signals that ultimately lead to activation of NFkB and TNFa. Mutations or polymorphisms in the TLR4 gene (gene map locus 9q32-q33) have recently been shown to be associated with both Crohn's disease and ulcerative colitis.

These discoveries have come hand-in-hand with the development of new biological therapies for controlling inflammation in Crohn's disease and other inflammatory diseases. The most important of these has been the development of TNFa antibodies/inhibitors such as Remicade (infliximab) and Enbrel (etanercept).

Additional genes contributing to Crohn's disease and ulcerative colitis will be discussed in subsequent articles in this series.

References


Explanation of Figure 1

Figure 1 shows a simplified scheme of the main components of the inflammation pathway. Several bacterial products (such as flagellin, a component of the whip-like flagella of bacteria, used for their movement) and components of cell walls (peptidoglycan and lipopolysaccharides) are sensed in the gut by several membrane-bound receptors, called Toll-like receptors (TLRs). There are 10 known human TLRs; for simplicity only 3 are shown in Figure 1. When activated, these receptors send signals that activate a key nuclear receptor, nuclear receptor-kappa B (NFkB), that in turn activates tumor necrosis factor alpha (TNFa), which then triggers inflammation. Several genes in this signaling pathway are now known to be altered in IBD (as discussed in the main article, adjacent). These gene defects include mutations in TLR4, NFkB, TNFa, NOD2/CARD15 (encoding a protein that normally acts as a brake on the TLR2 signaling pathway), and NFKBIA (a gene encoding a protein that acts as a represor of NFkB). While some of these names may be unfamiliar to many, readers will likely be more familiar with the medications that act in the same pathway to reduce inflammation, shown in blue in Figure 1. For example, 5-aminosalicylic acid (5-ASA) containing compounds (e.g. sulfasalazine and mesalamine (Asacol)) inhibit NFkB. Corticosteroids also are anti-inflammatory because they activate the glucocorticoid receptor (GR), which in turn down-regulates NFkB. The anti-inflammatory properties of ursodiol result from its binding to GR (see article: How Does Ursodiol Work? in this issue). Likewise, fibrates are anti-inflammatory because they activate the peroxisome proliferator-activated receptor alpha (PPARa), which in turn down-regulates NFkB (see article: Experimental Therapy: Fibrates in this issue). The tumor necrosis factor alpha (TNFa) inhibitors/antibodies such as infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira), block the inflammatory response mediated by TNFa. The latter biological medications have significantly expanded the arsenal of drugs available for treatment of inflammatory diseases such as IBD, psoriasis, and rheumatoid arthritis in recent years. A side-effect of the latter medications, however, is that they may increase the risk of certain infections such as tuberculosis. Mutations in the Toll-like receptor 2 (TLR2) gene have been implicated in susceptibility to tuberculosis (Ogus AC, Yoldas B, Ozdemir T, Uguz A, Olesen S, Keser I, Coskun M, Cilli A, Yegin O (2004) The Arg753Gln polymorphism of the human Toll-like receptor 2 gene in tuberculosis disease. Eur. Respir. J. 23: 219-223). Therefore, genetic screening for gene polymorphisms in the inflammation pathway may not only be important for elucidating the genetics of IBD, but also identifying patients at risk for developing side-effects from anti-inflammatory medications.


Acknowledgements:

We would like to thank Axcan Pharma (www.axcan.com) and Procter and Gamble (www.pg.com) for generously providing funds to support our conference in Denver in April, 2005. We are also indebted to all the speakers who have agreed to contribute to this conference; especially Dr. Gregory T. Everson and his colleagues from the University of Colorado Health Sciences Center (UCHSC), Denver, CO. We also thank all those members of the PSC support group, and their family, friends and care-givers, who have generously donated funds to the PSC Partners Seeking a Cure foundation.

Out of the Darkness

By Ricky Safer

As I lapse back into consciousness, I struggle to remember where I am. My mind feels like cotton; my throat feels battered, and I sense strange pains everywhere. I open my eyes to see the forced smile of my always-positive husband and the sad eyes of the rest of my family. “She’s up!” my husband utters in a voice that is trying too hard. I realize from afar that the ERCP that I had dreaded is over.

In my medicated state, all that I can decipher from the doctor’s update is “Ricky, you have PSC.” I close my eyes again, and each time that I reopen them, my family is still there. I keep asking the doctor the same questions over and over in my slurred voice. “Is there anything you can do for me?” to which he answers: “We can try to continue treating the symptoms, but there is no cure.” And then again and again I ask: “Where can I find more information on PSC? a support group?” to which he answers: “There is little available.”

As a person who has been a health and fitness fanatic my whole life, this sudden change of lifestyle was a rude awakening. The start of my journey with PSC was so lonely and confusing. I’m extremely lucky to have a loyal and loving group of family, friends, and colleagues who support me, but it wasn’t enough this time. I craved two things: more information on this dreaded disease and the support and wisdom of other PSCers who could guide me on this journey. When I finally discovered the Yahoo support group online, where I connected with a group of incredibly knowledgeable, compassionate, and supportive PSC patients and caregivers, I knew that my journey had taken a turn for the best.

Thanks to so many online members of the PSC support group who have helped in our project, our foundation is now established and growing quickly. We have created a vehicle that allows us to work together towards our ultimate goal of finding a cure for PSC. The mission of PSC Partners Seeking a Cure is to raise funds with which to research the causes and cures of PSC, to promote PSC and organ donation awareness, and to provide education and support to PSC patients and their families. Our first project, the national, now international, conference here in Denver will be a wonderful kickoff event. I am so eager to meet so many of my online colleagues. Those who can’t make it to the conference due to health, financial, or other reasons, will be greatly missed. Together, we will create programs that will help all of us who are affected by PSC. Every day, as I check the Yahoo support group e-mail posts, I remind myself that I no longer have to ask myself those two questions that I had posed to my doctor that fateful day. I look forward to a long and successful future for our foundation. Thank you over and over to everyone who has helped us!

Better to light a candle than to curse the darkness. Chinese proverb

Note to Readers

Articles in this newsletter have been written by persons without formal medical training. Therefore, the information in this newsletter is not intended nor implied to be a substitute for professional medical advice. Please consult with your doctor before using any information presented here for treatment. Nothing contained in this newsletter is intended to be for medical diagnosis or treatment. The views and opinions expressed in the newsletter are not intended to endorse any product or procedure.

Conference Reminder

The PSC Partners Seeking a Cure – 2005 Conference will be held in Denver, CO from April 29 – May 1, 2005. Please visit www.pscpartners.org for details of the conference and how to register. A discount registration fee is available until March 31, 2005.