



Johns Hopkins researchers discover key protein linked to transverse myelitis and multiple sclerosis

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Hopkins researchers have discovered a single molecule that is a cause of an autoimmune disease in the central nervous system, called transverse myelitis (TM), that is related to multiple sclerosis.

In a study published in the October issue of *The Journal of Clinical Investigation*, psychiatrist Adam Kaplin, M.D., Ph.D., an assistant professor at The Johns Hopkins University School of Medicine, and neurologist Douglas Kerr, M.D., Ph.D., also an assistant professor at Hopkins, showed that the levels of the protein, IL-6, are dramatically elevated in the spinal fluid of transverse myelitis (TM) patients.

Although the majority of TM patients suffer a single attack, 15 percent to 30 percent of patients go on to develop full-blown MS. TM evolves rapidly and without warning and usually results in permanent impairment, including weakness of the legs and arms, bowel and bladder dysfunction, pain and paralysis.

IL-6 is a chemical messenger that cells of the immune system use to communicate with one another. One of the cell types injured by high levels of IL-6 includes oligodendrocytes, which help produce the protective myelin sheath coating around nerve cells. The findings offer one possible mechanism responsible for demyelinating disorders, such as TM and MS, and may aid in the development of effective therapies against these disorders, the researchers say.

"This is the first time a single culprit has been identified as causing a CNS autoimmune disease," said Kaplin.

The researchers began investigating the protein IL-6 when they became aware that TM patients suffered from memory impairment and depression. IL-6 has been implicated in mood and concentration disorders.

"This discovery is a success story that begins with listening carefully to what patients are telling us about their suffering and then collaborating across disciplines to open up new avenues of investigation," said Kaplin.

"TM is related to other autoimmune disorders of the nervous system, including Guillain-Barré syndrome, MS and acute disseminated encephalomyelitis. This study may give us a foothold in understanding all of these disorders and how they are linked together. The benefit is, therefore, not only to those who are paralyzed by TM, but to those who have disabilities due to a variety of autoimmune disorders. We are actively using these findings to aid in developing future diagnostic, prognostic and therapeutic advancements," said Kerr, director of the Johns Hopkins Transverse Myelitis Center, the only center devoted to TM in the world.

Researchers analyzed 42 inflammatory proteins in the cerebrospinal fluid of both TM and healthy patients. They found that IL-6 was consistently elevated in TM patients' spinal fluid. Further, the level of IL-6 directly correlated with the severity of paralysis.

Using cell culture and animal studies, the researchers confirmed that elevated IL-6 levels were directly injurious to the spinal cord. They showed that spinal fluid from TM patients induced death of spinal cord cells when cultured in a dish and that IL-6, when infused in adult rats, induced paralysis. Under the microscope, tissue from IL-6-infused rats showed demyelination and injury of axons, pathology that was nearly identical to that seen in human patients with TM.

Kerr and Kaplin also deduced that the reason IL-6 elevations injure only the spinal cord and not other regions of the nervous system was because distinct regions of the nervous system have different responses to IL-6. They concluded that these different types of responses might be a part of why different autoimmune disorders of the nervous system affect distinct regions and cause distinct symptoms.

"When we started, we knew nothing about the bad players in this drama in the spinal cord of CNS autoimmune diseases - it was a classic murder mystery and we set out together to find out 'who done it'," said Kaplin. "We've answered who could have done it, and how, and where."

DIRECT-MS Comments- This finding is not a big surprise because IL-6 is one of the known inflammatory cytokines which would be expected to be present in abundance in the CSF of persons with TM and MS. It is of interest that IL-6 may be a major contributor to the damage. As usual the researchers greatly overstate the importance of their findings.

Multiple Sclerosis - cluster of genes on chromosome 6 only one that plays a significant role

September 22, 2005

A cluster of genes on chromosome six is the only one that plays a significant role in multiple sclerosis (MS), according to the most complete genetic study to date in the disorder, presented at the 130th annual meeting of the American Neurological Association in San Diego.

"Our results confirm the strong role of the major histocompatibility complex genes in MS, and provides a definitive statement that no other region of the genome harbors a gene with a similar overall influence on MS genetics," said Jonathan Haines, Ph.D, of Vanderbilt University in Nashville, Tennessee, who presented on behalf of the International Multiple Sclerosis Genetics Consortium.

"A detailed examination of the major histocompatibility complex is critically important," said Haines, who suggests that this study may have profound implications for the future directions of MS genetics research.

The major histocompatibility complex (MHC) is a cluster of genes that play a critical role in the recognition of cells in the body as belonging to the body, i.e., not intruders such as bacteria or other pathogens.

When this system of recognition breaks down, the immune system may mistakenly launch an attack against cells, as happens in MS. Researchers believe that some genetic variations in MHC genes make people more susceptible to whatever environmental causes also contribute to MS.

Haines is one of the founders of an international team of researchers from many institutions that collected genetic data on 730 families with more than one case of MS from Australia, Scandinavia, the United Kingdom, and the United States.

Previous studies have implicated the MHC, but also regions on other chromosomes, as harboring genes that increase MS risk. Haines suggests that these studies failed to include enough subjects.

"This is the largest genetic linkage study on MS, and the first to be done using the latest technology, which provides very detailed coverage of the entire human genome," said Haines. "Other genes may still play an important role in MS, but finding them will require using new genomic techniques."

Multiple sclerosis is an enigmatic disease of the nervous system and results in the loss of myelin, a substance that normally insulates nerve fibers and speeds electrical conduction through the fibers. Patches of inflammation (known as 'plaques') occur throughout the brain and spinal cord resulting in the loss of myelin and sometimes the nerve fibers themselves.

Depending on which nerve fibers are hindered, patients can experience problems ranging from weakness and clumsiness to numbness, visual disturbances, and even emotional and intellectual alterations. In some patients, MS manifests itself in cycles of relapse and remission and patients may show little sign of the disease between attacks.

A high density screen for linkage in multiple sclerosis Jonathan L. Haines, Ph.D.

This abstract describes the results of what we would consider to be the definitive multiple sclerosis linkage screen. The power of the study is so great that it is virtually certain that all susceptibility loci with effects large enough to be detectable by linkage have been found. The value of a definitive reliable linkage map cannot be overemphasized. The results from this study have profound implications for the future study of the genetics of this complex disorder and enable accurate minimum requirements to be determined for future studies. This is clearly a critical development in the field.

Ten centimorgan microsatellite map have been the standard tool used for whole genome linkage screening since the mid 1990's and to date 11 screens employing this methodology have been published in multiple sclerosis. However the scale and quality of the data in these studies is limited. In order to establish a definitive linkage map we have typed 4506 single nucleotide polymorphism markers in a set of 730 multiplex families from Australia, Scandinavia, the United Kingdom and the United States, which together provide 945 affected relative pairs. Highly significant linkage is observed in the region of the Major Histocompatibility Complex (lod score 11.7) and suggestive linkage is identified on chromosome 17 and 5. Ordered Sub-set analysis identifies a further locus on chromosome 19. The mean information extraction provided by the marker panel is 79.3% (range 42.4 - 91.3%) and the observed Mendelian inconsistencies suggests that within this data set the genotyping error rate is just 0.002%. These data have profound implications for the future directions of multiple sclerosis genetics research and suggest that previous efforts in this area are almost all substantially underpowered. In the future association studies will need to include at least 500-1000 cases.

DIRECT-MS Comments – This finding strongly supports the interpretation that MS is an autoimmune disease driven by cross-reactions between fragments of foreign proteins and self-antigens.

Economic Burden of Insufficient Vitamin D Greatly Outweighs Excess UV Light

September 20, 2005

A paper estimating the economic burdens from insufficient solar UVB irradiance and vitamin D and that from excess UV irradiance in the U.S. finds that the lost/foregone benefits greatly outweighed the actual adverse health outcomes. This study investigated the annual number of cases and deaths due to cancer, multiple sclerosis, and osteoporotic hip fracture that likely could have been prevented with sufficient vitamin D from UVB irradiance or oral sources as well as the number of cases and deaths from skin cancer and melanoma as well as cases of cataracts that likely have been prevented by avoiding excess UV irradiance. Economic burden values were then determined for these results.

It was estimated that about 50,000-63,000 annual cancer deaths in the U.S. (10 percent of all cancer deaths) could be prevented if all Americans had sufficient vitamin D. These findings are based on data in the Atlas of Cancer Mortality Rates for the United States, 1950-94, (<http://www3.cancer.gov/atlasplus/type.html>), but are also supported by a number of recent reports that vitamin D plays a very important role in increasing survival once cancer is discovered. These deaths greatly outnumber the annual number of deaths from melanoma (8000) and skin cancer (2000).

In the UK, the preventable cancer deaths with sufficient vitamin D may be as high as 20 percent since oral intake is low and vitamin D produced from solar UVB is much lower than in the U.S.

In addition, UVB irradiance and vitamin D also provide important health benefits in preventing or ameliorating such conditions or diseases as bone diseases and muscle pain, multiple sclerosis, type 1 and type 2 diabetes mellitus, high blood pressure, etc.

While more research is needed to check these results, there is already enough known about the health benefits of vitamin D to change public health policies now. In fact, conferences were held in the U.S. in the past couple of years to review the evidence relating to the health benefits of vitamin D and set new recommended levels. Final recommendations, however, have not been issued.

It is hoped that these results will provide further emphasis on the health benefits of UVB and vitamin D for maintaining optimal health and treating diseases and conditions. It is hoped that there will be a diminution of efforts to demonize UVB irradiance, as is being done in Australia, that additional foods such as bread be fortified with vitamin D, that guidelines for vitamin D increased, and that there be increased testing of serum vitamin D levels.

According to Cedric Garland, a coauthor of this study, and the first to link vitamin D to cancer risk reduction (in 1980), "This analysis estimates the number of cases and lives that could be saved, and the major economic savings that could result, from attempts to reduce incidence rates

of several important cancers by improving vitamin D status. More specifically, it estimates the reduction in incidence of these cancers that is likely to result from oral intake of vitamin D3, or no more than 10-15 minutes spent daily in activity outdoors in sunlight (not exceeding 0.75 MED), by persons whose skin type and personal history will allow. It also estimates a possible, although unlikely, increase in risk of skin cancer that might theoretically result, and places the potentially competing risks in context.

This comparison revealed that the vitamin D-based strategy for cancer risk reduction would have considerably greater benefits than risks."

DIRECT-MS Comments – The authors have documented the great costs associated with the “Avoid the Sun Campaign” which dermatologists have sold to the public. There can be little doubt that the maintenance of an adequate level of circulating vitamin D (100- 150 nmol/l) will greatly reduce the risk of numerous nasty cancers.

Genzyme and Schering AG Announce Interim Results from Trial of Campath for Multiple Sclerosis

September 16, 2005

Serious Adverse Events in Trial Require Comprehensive Risk Management Plan

Genzyme Corporation and Schering AG Germany today announced interim results from a Phase 2 trial comparing Campath® (alemtuzumab) with Rebif® (interferon beta-1a) for the treatment of multiple sclerosis. The results announced today derive from a pre-specified efficacy and safety interim analysis conducted after one year of treatment for all patients in the planned three-year trial. This review was conducted in conjunction with an independent data safety monitoring board.

Analysis of the primary endpoints after one year of treatment showed a large treatment effect in favor of alemtuzumab. Review of the data also showed that three confirmed cases of severe idiopathic thrombocytopenic purpura (ITP) occurred in the trial. Based on these results, and after consultation with the U.S. Food and Drug Administration, the companies will continue to collect both efficacy and safety data from this trial while preparing to initiate a Phase 3 trial. Dosing with alemtuzumab in this trial has been suspended while the companies work closely with regulatory authorities and clinical investigators to ensure that a comprehensive approach is in place to manage patient safety. Campath continues to be available in its current labeled indication for the treatment of B-cell chronic lymphocytic leukemia.

The Phase 2 trial randomized 334 patients with active relapsing-remitting multiple sclerosis at 49 medical centers in Europe and the United States. Patients were treated with alemtuzumab at one of two doses administered in once a year intravenous infusion regimens, or interferon beta-1a administered three times per week as indicated in its product label. The randomized, open-label trial compared the safety and efficacy of alemtuzumab with interferon beta-1a, examining two primary endpoints: the rate of relapse of MS symptoms, and the time to progression of clinically significant disability (time to Sustained Accumulated Disability at six months as measured by Expanded Disability Status Score [EDSS]). EDSS assessments were blinded and treatment groups were comparable at baseline for all key demographic and clinical parameters.

Analysis of the first co-primary endpoint showed that patients taking alemtuzumab at high and low doses experienced at least a 75 percent reduction in the risk for relapse after at least one year of follow up when compared to patients treated with interferon beta-1a. This difference was statistically significant in favor of the alemtuzumab patients at both the high and low doses according to the p-value (p=0.00267) assigned for the one-year interim analysis.

In the other co-primary endpoint, patients treated with the high and low doses of alemtuzumab experienced at least a 60 percent reduction in the risk for progression of clinically significant disability (p<0.05) when compared to patients treated with interferon beta-1a. This result did not achieve statistical significance according to the p-value (p=0.00015) assigned for the one-year interim analysis. Safety Results and Risk Management Program

In the trial, serious adverse events related to treatment occurred in two patients on interferon beta-1a, four patients on the low dose of alemtuzumab, and five patients on the high dose of alemtuzumab.

Idiopathic thrombocytopenic purpura is a condition in which patients experience a low platelet count that can result in abnormal bleeding. Of the three documented cases of ITP, two occurred in the high dose alemtuzumab group, and one in the low dose group. One case of ITP in the trial resulted in a fatality. In the two remaining cases, patients have responded to treatment and are being appropriately managed by their physicians using accepted treatment regimens.

As expected, common non-serious adverse events included infusion reactions in the alemtuzumab patients, and flu-like symptoms in patients using interferon beta-1a.

Genzyme and Schering's risk management plan for ITP has included notification of regulatory authorities, trial sites and patients, and consultation with a panel of hematologists with expertise in ITP to advise on risk management. The companies have moved forward to implement a series of provisions in the study, including more frequent hematological monitoring, and patient education about the signs and symptoms of ITP. Genzyme and Schering are also working to update informed consent forms, to conduct a thorough review of patient laboratory data, and to seek indicators that might help identify those at risk for developing these types of problems. The companies are currently in discussions with the FDA about what additional steps might be needed to protect patient safety.

Nearly all alemtuzumab patients in the trial have received their second year's dose. In the coming months, Genzyme and Schering will evaluate the necessity and timing of the third planned dose. Because the high dose appears to offer no efficacy advantage compared to that achieved by the low dose group, the companies will no longer use this dose.

"Based on these results, we will be moving this program forward with a tremendous sense of urgency," said Henri A. Termeer, chairman and chief executive officer, Genzyme Corporation. "Both companies are fully committed to advancing this treatment as intensively, thoughtfully and responsibly as possible."

"Our early analysis of efficacy from this study is very encouraging. We have a long history of commitment to advancing therapeutic options for patients with MS, and both companies will be working hard in order to move forward in the best interest of patients, balancing potential benefits with the possible risk of serious side effects," said Marc Rubin, MD, Member of the Board of Executive Directors, Schering AG, with responsibility for Development.

About Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic, debilitating disease in which the immune system attacks the person's brain and spinal cord. The disease causes a wide range of symptoms including fatigue, difficulty walking, numbness, and vision problems, and can progress to cause severe disability. Relapsing-remitting MS is the most common form of this disease.

About Campath

Campath (alemtuzumab for injection), is indicated in the United States for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy. Determination of the effectiveness of Campath is based on overall response rates. Comparative, randomized trials demonstrating increased survival or clinical benefits such as improvement in disease-related symptoms have not yet been conducted. Campath is a humanized monoclonal antibody that binds to a specific target, CD52, on cell surfaces directing the body's immune system to destroy malignant cells. It is the first and only monoclonal antibody approved by the FDA for the treatment of patients with B-CLL.

Phase 2 Trial Detail

A total of 334 patients in the trial were randomized to receive either a low dose of alemtuzumab (12 mg/day for five days), a high dose of alemtuzumab (24 mg/day for five days), or interferon beta-1a (44 mcg administered three times per week). At 12 months, patients on alemtuzumab received a dose of 12 or 24 mg/day for three days. Data reviews are scheduled at 12, 24, and 36 months for the co-primary endpoints and a series of secondary endpoints.

DIRECT-MS Comments – Another fine example of a killer drug that the pharmaceutical industry would like to sell persons with MS. In the previous Phase I trial of Campath 45% of the subjects got autoimmune thyroiditis. That did not deter the researchers from starting the phase II trial that has already killed one subject and seriously damaged others. If a Phase III trial gets off the ground, it will likely produce deadly cases of PML, the brain disease that killed people in the Tysabri trial. Sadly the biggest boosters of this drug are researchers at Cambridge University, a supposed centre of higher learning.

Does the Pill Protect Against Multiple Sclerosis?

September 13, 2005

Across the world, more than 100 million women rely on the pill to prevent pregnancy. Now, new research shows it may be doing something else for their health.

Researchers from the Harvard School of Public Health in Boston, say the pill may help prevent multiple sclerosis, an autoimmune disease that affects the central nervous system. In a study comparing 106 women with newly diagnosed MS to about 1,000 matched women without MS, researchers found the incidence of MS in women who used oral contraceptives was 40-percent lower than in those who didn't use them.

In earlier animal studies, estrogen delayed the onset of MS and also eased the course of the

disease, suggesting oral contraceptives, which contain estrogen, may affect the risk of getting MS. Other research shows pregnancy and the period directly following pregnancy may also play a role.

Not only did study authors find those on the pill had a lower risk of developing MS, they also found women had a higher risk of developing first symptoms of MS in the six months following a pregnancy.

Researchers conclude, "Recent [oral contraceptive] use and, possibly, current pregnancy are associated with a lower risk of developing MS. On the contrary, the postpartum period confers a higher risk of MS onset. Our findings suggest that high levels ... estrogens from [oral contraceptive] use and of ... estrogens during pregnancy may delay the first clinical attack of MS."

DIRECT-MS Comments – This is another useful finding from the Harvard researchers who are mining the Nurses Database to discover relationships between environmental factors and MS. Higher estrogen likely lowers the risk of MS but unfortunately it likely increases the risk of diseases such as breast cancer. The main contribution of this study is that it adds to our understanding of the role of hormones in MS pathogenesis.

Spanish scientists develop a cellular therapy for rheumatoid arthritis and multiple sclerosis

2005-09-09

A research team at the Institute of Parasitology and Biomedicine of the Spanish National Research Council (CSIC), in Grenade, has successfully developed in mice a cellular therapy for two major autoimmune diseases: rheumatoid arthritis and multiple sclerosis. The scientists succeeded, in both experimental models, in making the symptoms disappear and inducing a reversion of the degenerative process. The results of the research were published this week in the digital edition of the Proceedings of the National Academy of Sciences (PNAS).

Autoimmune diseases occur when the immune system that normally protects the body from disease and infection attacks itself. Autoimmune diseases can affect many parts of the organism, like the nerves or the muscles, and cause significant and chronic morbidity and disability.

The therapy uses a certain type of cells (dendritic cells), which when injected in animals affected by these disorders, generate T regulating (Tr) cells, responsible for the maintenance of immune tolerance. CSIC scientist and lead of the research team, Mario Delgado, explains: 'the analysis of the cellular mechanisms has unveiled that these dendritic cells induce new Tr cells in the treated animals, and that these cells specifically neutralise the immune cells that attack components of the joint, in the case of rheumatoid arthritis, or the myelin covering the nerves, in the case of multiple sclerosis'.

The therapy was also effective with Tr cells generated in vitro. In both cases, the response was induced by using a known immunosuppressive neuropeptide, the vasoactive intestinal peptide (VIP), a protein that is produced by lymphoid as well as neural cells, that the scientists know acts like a powerful anti-inflammatory agent. The research team lead by Dr Delgado has studied the

use of the VIP on a multiple sclerosis model for ten years.

The therapeutic process would start by extracting blood or marrow cells from the patient suffering the autoimmune disorder. These cells would be treated with VIP so that they turn into dendritic cells. Finally, these cells could be injected in the patient so that they induce new Tr cells and the immunological tolerance is recovered. An alternative therapy could be based on using these regulating dendritic cells in vitro to generate the Tr cells that could be then injected into the patient.

Dr Delgado, explains that 'the results with animals are very promising', although, he is cautious about its eventual use in humans, warning that this would be a 'customized personal cellular therapy implying high costs'. Its use could be justified though as some degenerative disorders do not have any alternative effective treatment. Multiple Sclerosis (MS) is a chronic and severe neurological disease, largely diffused all over the world. MS preferentially affects young adults and has high social costs, representing a real emergence at both clinical and social levels.

To download the abstract of the PNAS paper, please consult the following web address:

<http://www.pnas.org/cgi/content/abstract/0504484102v1>

DIRECT-MS Comments - Therapies that increase the suppressor capacity of the immune system hold a lot of promise and this strategy of increasing regulatory dendritic cells may one day prove to be an effective therapy for MS.

MS Vaccine Shows Promise

Aug 29, 2005

Some exciting news on the horizon for multiple sclerosis patients. Scientists are testing a vaccine that seems to halt the progression of the disease. It's hoped that 1 day the vaccine could reverse the effects of MS. Losing strength and coordination is a big problem. Sue Carlson was diagnosed with multiple sclerosis 10 years ago.

Sue Carlson, multiple sclerosis patient: "It came on suddenly and I was deteriorating quickly." Sue's eyesight was failing, she was falling down and was forced to cut her workload in half, but she found hope in a clinical trial for a new vaccine called Neurovax. Sue Carlson: "I had been on Neurovax for about 3 months and I realized things were starting to come back." In fact, sue says her symptoms have gone away. Arthur VandenBark, PHD. Neuroimmunologist: "We've had a few examples where we've had very, very good responses, and many other examples where we've been able to stabilize the disease so it doesn't progress any further."

Scientists discovered that MS patients lose the foxp3 gene. Simply put, Neurovax restores foxp3 levels by expanding healthy cells which in turn block the bad cells that have become active.

Arthur VandenBark: "When we activate the regulatory cells, we're helping them to produce these anti-inflammatory factors."

If after more trials Neurovax proves successful, for some, combating MS could 1 day be as simple as a shot in the arm. Arthur VandenBark: "Probably give them maybe 3 at the beginning once a month and then follow every 3-6 months with a booster injection." Early results suggest

Neurovax might be able to treat MS in both early and late stages, which may be why Sue Carlson never misses a day of work.

DIRECT-MS Comments – This is another therapy that increases the immune suppressor capacity of the immune system and thus has promise.