

INTRAVENOUS IMMUNOGLOBULIN THERAPY AND NARCOLEPSY

by Regina Patrick RPSGT



Narcolepsy is a syndrome characterized by periods of overwhelming sleepiness; hypnagogic hallucinations; sleep paralysis on awakening or going to sleep; and cataplexy (sudden total loss of skeletal muscle tone often triggered by intense emotions). Scientists are not sure why narcolepsy occurs but recent studies suggest that it may be an autoimmune disorder. Researchers have found that hypothalamic cells which produce hypocretin (an excitatory hormone that helps maintain wakefulness) are inexplicably destroyed in narcoleptics; the gene HLA-DQB1*0602 which is found in a high percentage of narcoleptics belongs to a class of genes (HLA-DQB1) associated with other immune disorders; about 15% of narcoleptics develop symptoms after a febrile illness which may have been viral in nature; and about 25% of narcoleptics have signs of an ongoing immune response as evidenced by minor abnormalities in the cerebrospinal fluid such as lymphocytosis (excessive amount of lymph cells) or increased amounts of protein. With this in mind, sleep researchers have begun investigating treating narcolepsy by modulating the immune system. Corticosteroids have had inconsistent success but another treatment – intravenous immunoglobulin (IVIG) therapy – appears more promising.

Globulins are a class of proteins contained in blood serum. They are divided into three groups – alpha-globulins, beta-globulins, and gamma-globulins. Most gamma-globulins and some alpha-globulins and beta-globulins mediate immune activities.

Immune-modulating globulins (i.e., immunoglobulins [Ig]) are also called antibodies. Immunoglobulins bind with an antigen (a harmful foreign substance or organism) and once bound to the antigen an immunoglobulin may stimulate white blood cells to actively destroy the antigen; or it may bind with the antigen in such a way that it is easy for white blood cells to digest the antigen; or it may trigger white blood cells to release substances which in turn destroy the antigen. Defective synthesis or impaired release of immunoglobulins can result in low levels of the proteins in the blood. A person consequently has impaired immune function and may be subject to frequent infections, anemias, and cancers such as leukemia. Replacing immunoglobulins can thwart this process.

The therapeutic use of IVIG became widespread after 1952. That year, Odgen C. Bruton noted that gamma-globulin injections in a young boy with low gamma-globulin levels reduced the boy's susceptibility to repeated pneumococcal infections which had not responded to other treatments. At the time, Bruton was unclear whether the boy's low gamma-globulin level was the result of his infections or the result of an autoimmune process. To test this, he monitored the boy's blood level of gamma-globulins for a six week period after he had recovered from his last infection; the boy's levels of gamma-globulins slowly disappeared. This indicated that the boy could not make his own gamma-globulin. Bruton gave the boy monthly doses of gamma-globulin replacement therapy (i.e., IVIG therapy) to ward off susceptibility to infections. Previous to IVIG, the boy had had 19 bouts of pneumococcal infection within a four year period but during IVIG therapy he remained symptom-free. Subsequently, IVIG therapy became a standard treatment for people with immunoglobulin deficiency disorders.

The immunosuppressive activity of gamma-globulins became apparent in 1981 when Paul Imbach and coworkers were using IVIG therapy to treat gamma-globulin deficiency in children. Two of the children also had idiopathic thrombocytopenic purpura (ITP), a hemorrhagic disorder that involves the autoimmune destruction of platelets. Imbach noted that the platelet levels of the two patients rose resulting in their recovery from the symptoms of ITP (e.g., easy bruising, bleeding gums, nosebleeds). The rise in platelet levels suggested that the gamma-globulins used in IVIG therapy were suppressing the immunologic destruction of platelets. This discovery stimulated research in investigating the use of gamma-globulins to suppress the immune response in other disorders that involve faulty immune function. The use of IVIG therapy for narcolepsy is an outgrowth of its use to modulate immunodestructive activities occurring in other neurological disorders such as multiple sclerosis and myasthenia gravis.

European scientists Michel Lecendreux and coworkers in 2003 were the first scientists to use IVIG to treat narcolepsy in a 10 year old boy. Two months before treatment, the boy had suddenly developed narcolepsy with cataplexy (triggered by laughter) but he did not have symptoms of sleep paralysis or hypnagogic hallucinations. Brain imaging showed that no lesion existed that could explain his sudden symptoms. A spinal tap revealed that the boy's cerebral spinal fluid had undetectable amounts of hypocretin further validating

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ing a narcolepsy diagnosis. With the thought that the short duration of symptoms may not have allowed extensive autoimmune destruction of hypocretin-producing cells to occur, the researchers decided to use the immunosuppressive activity of IVIG to block any further autoimmune destruction of the cells and restore proper immune function thereby reversing symptoms of narcolepsy.

Lecendreux et al. treated the patient with immunoglobulin G (IgG, one class of gamma-globulin) intravenously for two days. They then administered intravenously the glucocorticoid prednisolone for three weeks. They noted that three days into treatment, the boy's symptoms of cataplexy and sleepiness were improved. Two months after the initiation of treatment, the boy had had only four partial cataplectic attacks (affecting only the facial muscles) but his sleepiness was increasing. At this point prednisolone was stopped due to side effects (e.g., acne, weight gain) and modafinil was prescribed to counteract sleepiness. Five months after diagnosis, all of the boy's symptoms had returned although modafinil continued to improve sleepiness.

From these results, Lecendreux et al. concluded that, when used soon after diagnosis, both corticosteroids and IVIG could be useful in countering the apparent abnormal immune activity in narcolepsy. They also speculated that low levels of hypocretin in narcolepsy may not be connected to the immune-mediated aspect of the disorder since a second spinal tap done two months after beginning immunosuppressive treatment still revealed undetectable amounts of hypocretin in the boy's cerebral spinal fluid.

French researchers Yves Dauvilliers and coworkers studied the effect of IVIG therapy in a group of narcoleptics in their 2004 study. The study involved four narcoleptic subjects – three of whom were treated within months of being diagnosed with narcolepsy. (The IVIG preparation contained IgG.) The subjects reported reduced frequency and severity of cataplectic attacks during 7 months of IVIG therapy. They did not use any medications to counteract cataplexy while on the treatment. Dauvilliers et al. concluded that IVIG may be beneficial as a treatment especially if used early with the onset of narcolepsy symptoms.

Scottish physician Sameer Zuberi similarly studied the effect of IVIG therapy in pediatric narcoleptic patients but had inconsistent results. The first patient was an 8 year old boy who had suddenly developed severe symptoms of sleepiness to the point of having to drop out of school. Zuberi decided to try IVIG after standard treatments had failed. Within about a month of beginning IVIG therapy, the boy's symptoms resolved. This lasted about 3 months at which point he was given another dose of IVIG. Encouraged by these results, Zuberi tried IVIG therapy on a teenaged female who had had symptoms of narcolepsy since toddlerhood. Her symptoms, however, did not improve with the therapy.

This discrepancy in Zuberi's results may be related to the length of time the subjects had had symptoms. It may be that the longer duration of symptoms in the female allowed a longer process of autoimmune destruction to occur which in turn hampered the effectiveness of IVIG therapy. For this reason, Dauvilliers cautions that early diagnosis and treatment of narcolepsy may modify the course of the disease.

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IVIG therapy is opening up new avenues for scientists to explore. For example, IVIG appears more beneficial for reducing cataplexy episodes than for reducing sleepiness which suggests that the therapy may somehow be thwarting immune processes involved in cataplexy but not those involved in sleepiness; IVIG therapy does not restore hypocretin levels in the cerebral spinal fluid which suggests that either autoimmune destruction of the cells is irreparable or the destruction of the cells may not be the result of an autoimmune process. Investigating these and other findings of IVIG therapy may help scientists understand what sets an autoimmune process in motion in narcolepsy and how to thwart it.

Current treatments for narcolepsy involve the use of stimulants to maintain wakefulness; antidepressants to stave off cataplexy; or gamma-hydroxybutyrate (GHB) which does both. Side effects of the drugs such as addiction, insomnia, tremors, and sensations of panic can make effective control of symptoms difficult in narcoleptics. IVIG therapy, when more clearly understood, may offer a new treatment option for people with narcolepsy.

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