

A CAREER DEVOTED TO THE BATTLE AGAINST DEADLY BRAIN DISEASE

One in every thousand children has abnormalities of the white matter of the brain. Many of these disorders are genetically determined and progressive, associated with a fatal outcome. Paediatric neurologist Marjo van der Knaap has been investigating childhood white matter disorders for the past 25 years and has achieved some important breakthroughs that clear the way for an effective therapy. She hopes to see the search for a cure to be successful in her lifetime.



By Anita Mussche

"Of course I'm upset every time a child dies. It breaks my heart to have to tell parents that their child has a leukodystrophy, and only has a short life ahead. But my job is to support them in their hour of need, to explain how we are going to deal with each and every problem. When I do that, I make the situation bearable for the parents. If I give way to my emotions, I cannot perform this role properly." Marjo van der Knaap (born 1958) is professor of Paediatric Neurology at the VU Medical Centre in Amsterdam, where she performs research on white matter disorders in children. Leukodystrophies have catastrophic consequences, but Prof. Van der Knaap sees this as a challenge: "I'm not the kind of person you can get to do fundamental research on the common cold. Leukodystrophies are a terrible problem. We have to find a solution for them."

ultrafast conduction of the nerve impulses. If something goes wrong with the white matter, the different parts of our brain can no longer communicate with one another and with the rest of the body. Neurological function is progressively lost, and the patient dies young.

FROM MRI SCANS TO TREATMENT

Marjo van der Knaap has been working on childhood white matter disorders since the late 1980s. At that time, there was the field of multiple sclerosis, an inflammatory white matter disorder, but apart from MS the "white matter field" did not exist for medical researchers. In 2008 she received the Spinoza Prize of the Netherlands Organisation for Scientific Research (NWO) – sometimes called the Dutch Nobel Prize. This prestigious award consists of research funding worth one and a half million euros. Marjo van der Knaap discovered that she could use MRI scans – a new technique in the 1980s – to diagnose white matter disorders.

"I could have done all kinds of other things, but I always knew I was going to be a scientist"

At that time it became clear that in more than half of the affected children no specific diagnosis could be established. She then started to use MRI to define novel white matter disorders, one of which was named the "Van der Knaap syndrome". Working with her research group, she identified multiple genes that, when mutated, cause the newly defined diseases. She then initiated investigations to understand disease mechanisms.

Despite all the important discoveries Marjo van der Knaap has made, there is still no cure for these diseases. But she is doing her best to find one. She gave part of her Spinoza Prize money to a stem cell laboratory run jointly by VU University Amsterdam and VU University Medical Center, since stem cell therapy could be the basis for the treatment she is trying to find. Another new field for her to explore. "Yes, I thoroughly enjoy discovering new facts, finding my way in new territories. I could have done all kinds of other things, but I always knew I was going to be a scientist."

The Spinoza Prize gave her recognition and the money to continue her research. But she says she is not really interested in status or ambition. "Ambitious people want reach something, for instance status or a position, and become frustrated if it takes too long. I'm not like that. I've got an inner drive. I want to work, do things. I do all I can, and I'll see what comes of it."

WHY IS THE BRAIN AFFECTED, AND NOT THE LIVER?

Why is there still no cure, if we know which genes are mutated in a particular disease? "Because the genes mutated in the disorders we are working on affect very basic processes in the body that are not easily fixed. For instance, we do much work on a disease called "vanishing white matter". The genes mutated in this disease belong to the class known as housekeeping genes, which play an important role in every cell of the body. These genes are involved in the regulation of protein production in the body. In general, protein production must be down-regulated in response to fever or other stress situations. This regulation is disturbed in patients with vanishing white matter, making them sensitive to stresses like fever and minor head trauma. "Why in this disease, only brain cells – and more specifically the cells of the white matter – are damaged, and not for example liver cells, we do not yet understand."

Prof. Van der Knaap works on different fronts. She and her fellow-researchers keep on trying to understand the mechanisms underlying the development of leukodystrophies. She is also testing the effect of a wide range of drugs on brain cells. And then there is the new stem cell laboratory, where researchers try to get stem cells that have been programmed to develop into brain cells to establish themselves at the right spot in the brain, divide and repair the white matter.

But they're not there yet. "Far from it. It may well be that we won't discover the mechanisms underlying white matter disorders during my lifetime. I would like to think that I will be able to keep an eye on things down here on earth from somewhere up there in the sky, so that I will finally be able to say, 'Oh, that's it, is it?'"

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MOMENTS OF ILLUMINATION

Still, she has made her fair share of discoveries already. "That's what I like about science: it offers you those moments of illumination." She was writing a review article on a particular form of leukodystrophy for a journal not long ago. They had asked her to

include a figure illustrating the way the disease works. "I really wasn't keen on the idea at all: we don't have the picture clear yet, so any ideas I put into the figure are almost certain to turn out wrong in the long run. I was sitting looking at the figure one Saturday, when I had a flash of inspiration: Wow, that's how it works! I said to myself." She tried to phone her colleagues from the research team to share the good news, but there was no one there: it was the weekend, after all.

In fact, Saturday is her favourite day of the week for working. "I sometimes say that I only work one day a week and that's Saturday, because there's no one to disturb me then. Andre Geim, who shared the Nobel Prize for Physics in 2010, said in the Dutch evening paper NRC that the harder you work the more likely you are to make chance discoveries, and that's true." She works sixty to seventy hours a week. In her free time she reads or works in the garden, and she always puts on music as soon as she gets home.

I'M ADAPTABLE

Although some people might think that leukodystrophies are a depressing subject, Prof. Van der Knaap enjoys her work immensely. "Science was my salvation: I was a bit of a nerdy child, with glasses and a sports deficit disorder. I was a failure in sports, no one wanted me on their team when they were choosing sides, and they only gave me a pass mark on my report for PE out of pity," she laughed. But she sucked up all the knowledge that came her way at school. She still finds that surprising. "I'm one of six children, and none of the others is like me." She started studying Classics at university, but when realizing that this would most likely make her a teacher, she switched to Medicine because it offered better career perspectives. Her initial intention had been to specialize in internal medicine, but she couldn't get a residency for that. She could for neurology. "So I thought, that's fine too. I'm flexible. I am not stuck on one thing."

Marjo van der Knaap takes insights from neurology, radiology, pathology, genetics and molecular biology. You can only understand a neurological disease if you know a lot about different disciplines, in her opinion: "Some of the specialists at the lab know a good deal more about particular subjects than I do, and I'm glad they do. But I still know enough to tell when they're talking nonsense."

SOURCE OF INSPIRATION

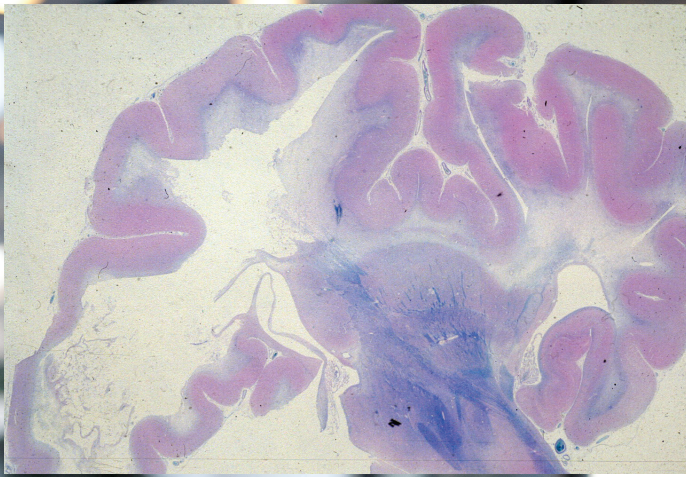
At least two-thirds of her working days are spent on research but clinical work has always been her source of inspiration, she stresses. "I have never worked on problems that I didn't encounter first in my medical practice. My source of inspiration is the people who consult me as a physician. I ask myself what exactly the nature of their complaint is." The practice of medicine keeps her feet on the ground. "I might become a fanatic, if I spent all my time on research. I need both, science and medicine, to keep me balanced." >>



The parents of a girl with vanishing white matter disease and Prof. Marjo van der Knaap on the Dutch TV talk show Knevel & Van den Brink.

DYING YOUNG

White matter facilitates the different parts of the cerebral cortex, also known as the grey matter, to communicate with one another and with the rest of the body. The cerebral cortex is the outermost layer of the brain and is made up of nerve cell bodies and short nerve fibres. The white matter, situated in the middle of the brain, consists of billions of nerve fibres, the axons, each surrounded by a layer of a fatty substance known as myelin, whose main function is to ensure



TERRIBLE DISEASES, BUT THE TALK WITH THE PATIENT AND THE PARENTS NEEDN'T BE ALL DOOM AND GLOOM

She has made spectacular discoveries in her research, but she still can't offer her patients a cure. How does this affect her relationship with them? "Well, sometimes you have to tell parents that their child has a very serious disease and does not have more than a few years to live. It goes without saying that the family needs some time to come to terms with this message. But then they return to some kind of normal life. They come to see me in the hospital, I see how the child is getting on and we crack a few jokes. I enjoy working with my patients, and the atmosphere when they come to consult me is not dismal or depressing – on the contrary!"

She realizes how important her research is for the parents and children in question. "Parents may say 'I have come to terms with the fact that there is no cure for this disease and that my child will die. But one day there should be a cure to help other kids'. I have a deep admiration for the people who say that they can accept that there will be no cure for their children." It must be very difficult then to see how slow the progress towards a solution is. "The funny thing is that progress may seem to be terribly slow from day to day, but in retrospect it's amazing how much progress has been made. You can see insights growing and taking form over the years. No, I am very happy with every little step forwards we take in our scientific endeavours."

THANKS TO THE LOW THRESHOLDS AT VU UNIVERSITY AMSTERDAM

Marjo van der Knaap started her career as a neurologist and then paediatric neurologist in Utrecht. Her interest in the possibilities offered by MRI led her to do an internship at VU University Amsterdam, where she carried out research on various white matter disorders. When there proved to be no permanent position for her in Utrecht, she applied for one at VU University Amsterdam. "Otherwise I would have stayed in Utrecht. It's difficult to know how my career would have turned out then. The great thing about VU University Amsterdam is the relatively low-threshold research environment here. Though I was trained as a neurologist, I did genetic research, and no one raised an eyebrow. I had no problems getting access to the MRI scanner either." Prof. Van der Knaap works closely with the Center for Neurogenomics and Cognitive Research (CNCR), the main focus for neurobiology, clinical and fundamental neuroscience and psychological research at VU University Amsterdam and VU University Medical Center. This is just the kind of environment Marjo van der Knaap needs for her interdisciplinary brain research. "Neuroscientists know a lot about things that I never had much contact with in my medical career – how fundamental biological processes work, for instance. We can teach one another a lot."

For further information (in Dutch), visit www.vumc.nl/afdelingen/Center-White-Matter-Disorders/