Pompe's Disease
World success with a setback: laborious production of the medicine

Research at the *Erasmus Medical Centre* in Rotterdam on Pompe's Disease has resulted in a world success: it has been proven now that the so-called enzyme replacement therapy (ERT) works. But the road to that success has known many setbacks.

Pompe's disease is a congenital disease. From a defect in the DNA a patient lacks the important protein that breaks down *glycogen* in healthy persons. With Pompe patients that substance stores itself mainly in the muscle cells, which will thus be damaged and cause functional disorders.

The disease belongs to a group of so-called lysosomal storage diseases (LSD's) and can cause severe muscular weakness. Because the respiratory muscles as well as the heart muscles are affected the babies will ultimately be dependent on respiratory support. They seldom live beyond their first year.

The disease appears also in less severe forms. It can manifest itself after several years or even at a much later age. The disease is rare: in the Netherlands there are only about a hundred patients in a population of 16 million.

Speed is essential

The treatment consists of the administering of the enzyme which the patient lacks. Which is done by a weekly infusion. As a first in the world the Erasmus MC started five years ago this ERT with four babies. Paediatrician *Dr. Ans van der Ploeg* looks back: "Primarily we wanted to know if the therapy worked. Now we know that that is the case. Also we wanted to know which phase is the best to start the treatment. As early as possible or when the disease is already progressed. It has been shown that you have to start early. When the muscles are already damaged, the affected muscle strength can not be repaired fully. The treatment had a phenomenal effect with some patients. One of them is five years old now. He still has mild symptoms of the disease, but he can walk, ride his bicycle and run. A man of 32, who, because of the illness was only lying in his bed, is back in his wheelchair and can undertake activities with his children again. Patients can look to their future again."

Rabbits and Hamsters

The ERT could be started at the time because the Dutch pharmaceutical company *Pharming*, in cooperation with researchers from the Erasmus MC, had developed a method to produce the enzyme that Pompe patients lack in the milk of genetically modified rabbits. Unfortunately the success was short-lived. Pharming went bankrupt about two years ago. The production was taken over by the company *Genzyme*. Earlier both companies decided to adopt another production method: with ovary cells of the Chinese hamster. This was simpler and cheaper according to these companies.

Setbacks and misfortunes

The expectations of "simplicity" did not work out: the company had difficulties to start the production. Fortunately there was still a supply of rabbit-produced medicine, so that the patients still could be treated. Meanwhile the new patients got the new medicine, which came slowly available. "The parents were very worried" tells Dr. van der Ploeg "First the older patients were transferred to the new medicine. With the babies we did not dare to take the risk. Because the whole balance in their bodies is much more fragile. Also there was a discussion about the dosage of the new medicine. A physician in the USA claimed that the new medicine was much more effective and could be administered in much lower dosages. Without any scientific proof. And on the basis of our own results we were very doubtful. We also saw that our older patients were deteriorating with less medication. *Genzyme* finally responded to our arguments. Now the babies get the same dosage from the new medicine as with the old one".

Strongly involved

All obstacles caused many worries and insecurity with the parents of the patients, was also observed by *Dr. Hannerieke van der Hout*, who recently was awarded her doctor's degree for her research on the ERT. Her article on the medicine derived from rabbit's milk was published in the summer of 2000 in the medical journal *The Lancet* and became world news. That, and also the rest of her research period, she experienced as a very impressive period. "Because only four babies were in the programme, I have been very intensely and personally involved with the parents. It was very special that I was allowed to guide and support them during the whole process. Also the people with whom I cooperated were very committed. Biochemist *Arnold Reuser* came regularly from his laboratory to the clinic to see how the patients were doing. And Dr. van der Ploeg has put a lot of energy in talking to and consulting with the parents and pharmaceutical companies."

Protection needed

The history of Pompe's disease also shows how vulnerable the position of a patient can be. Dr. Van der Hout has recognized that situation during her research: "The development of a medicine has two aspects. On the one hand there is the physician who wants to treat a patient and the patient who wants to get well. On the other hand the industry, searching for an effective treatment that must cover the costs of development and production. We expected that a successful treatment of the patient would also result in a successful product for the industry. That proved not to be the case. A situation of tension was developed what resulted in painful and difficult situations. Maybe there should be an independent committee to supervise the development of drugs. The committee should have the authorisation to protect the patient in one way or another when situations like these arise."

Discussions still continuing

How are the treatments to be continued? Because the medicine is not yet registered (approved) it is not freely available yet. Genzyme is conducting trial studies which are necessary for approval and registration. There is sufficient medicine for the treatments of patients to take part in the trials, but not yet for all patients world wide. Genzyme expects that the medicine will be available for all patients within a few years. But until then not all the patients can be treated.

In the mean time the research for the causes of the disease will continue, tells biochemist Dr. Arnold Reuser, who did his doctorate research on this subject already in 1977. In February this year there was another ceremony for a doctoral degree at the *Erasmus University* in Rotterdam and there are three additional promotion researches. This emphasises the position of the Erasmus MC in the field of Pompe's Disease.

Dr. Reuser: "The last few years we have concentrated on the DNA defects and how those translate into the protein defects. We try to find a relation between those defects and the life expectation of the patient. We have investigated in the past the dosage in mice. This resulted in the conclusion that higher dosages were needed than we had assumed. And giving a higher dosage to our patients has proven to be successful."

World wide databank

The clinical research at the Erasmus MC also continues, with children as well as with adults. Paediatrician Dr. van der Ploeg communicates regularly with *Genzyme* but also world wide with researchers and patient organisations. "That's why we can start a study shortly on the natural course of the disease. We want to investigate how muscle strength and respiratory functions are developing. With those data we are planning to establish a world wide databank. Not only for Pompe's disease but also for other storage diseases. Recently we started with the treatment of another LSD: *Hurler's disease*. In cooperation with medical centres in France, Germany and England and with Genzyme we investigate the efficacy of the medicine *Aldurazyme* with children under five years of age.

With older patients with a milder form of the disease the efficacy of the ERT has been proven. The Association of Medical Insurers in the Ne therlands will reimburse the treatment through a special arrangement."

At the bedside

The last couple of years have been very intense, comments Dr. van der Ploeg, looking back. "In our hospital we have been at the bedside of our little patients in the IC-unit while they were given an infusion. The parents also have been through an emotional roller coaster. Their child's illness is difficult in the first place, but they can accept that, because it is "nature's way". But the difficult situation caused by the problems with the production of the enzyme was much harder to accept.

'Enormous impact'

"That my doctorate research would be an impressive period was to be expected. But the enormous impact that it had I could not possibly have foreseen," tells paediatrician Dr. Hannerieke van der Hout. "It is very moving to see a patient walk again after a certain time. Or to realise that a kid of five that now goes to school would have died as a baby without our research."

At first the parents were torn between hope and fear. Fear to lose their child before it's first birthday. Hope that the new treatment could save their baby. "The predicament of being torn between these sentiments has moved me very much," continues Dr. van der Hout. "When one of our patients started to turn on his own strength, we could hardly believe it. But when this patient and another learned to sit, we slowly dared to start to think positively."

Unfortunately not all children with Pompe responded equally well. Some were already too severely affected to turn the disease around. One patient died. "It is terrible to witness parents lose a child who fought so hard. Her death struck all of us, the other patients in the trial as well as us doctors.

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Translated from Dutch: Gezinus Wolters (VSN) (www.vsn.nl)