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Liver cell transplantation for the treatment of innate urea cycle defects

Liver transplantation is the only life-saving therapy available to patients suffering from genetic defects of the urea cycle. However, newborns cannot be transplanted with a donor liver. The injection of liver cell suspensions into the liver of sick babies through the portal vein can substitute the lack of enzyme activity, hence preventing brain damage until such time as liver transplantation becomes possible.

Defects in enzymes involved in the urea cycle are one of the most dangerous metabolic disorders in newborns and infants. Toxic ammoniac (NH3) in the liver is created when proteins are degraded, and defective enzymes are unable to convert this into nontoxic urea. Urea is excreted through the kidneys. Enzyme defects generate elevated ammoniac concentrations in the blood (hyperammonemia), leading to irreparable brain damage, which depending on the severity, can lead to developmental disorders and even death.

Bad prognoses for newborns with enzyme defects

Genetic urea cycle defects are regarded as rare orphan diseases; only one in around 8,000 children is affected by this disease. The insufficient detoxification of ammoniac could be due to defects in the activities of a range of enzymes involved in the urea cycle. Enzyme activities can be diagnosed with biochemical tests. Ornithine transcarbamylase (OTC) deficiency is the most common urea cycle disorder; other urea cycle disorders include carbamyle phosphate synthetase I (CPS-I) deficiency and argininosuccinate synthetase (a disorder known as type I citrullinemia) deficiency which is characterised by the accumulation of ammoniac and citrulline in the blood. Effective treatment depends decisively on the early diagnosis of the disease – directly after birth or during the first days of a baby's life. However, because it is so rare the disease is hardly ever detected. It is possible that experienced paediatricians never come into contact with this disorder in the course of their entire professional career.

Although the prognosis of children with innate urea cycle defects has improved thanks to medical treatment and strict diets, many of the children nevertheless suffer brain damage and developmental disorders, or die at a relatively young age. Attempts to replace the defective enzyme through gene therapy with viral vectors were abandoned in 1999 following the death of a young boy. "At present, the only long-term life-saving therapy for patients suffering from severe

Prof. Dr. Georg F. Hoffmann, Medical Director University Children's Hospital in Heidelberg

urea cycle disorders is liver transplantation - however, this is not currently possible for newborns," explains Prof. Dr. Georg F. Hoffmann, Medical Director of the University Hospital in Heidelberg. But now there may be a way out of this tragic dilemma.

Cell therapy for the stabilisation of the metabolism

Hoffmann, who is one of the pioneers of a screening method used to screen all newborns for the presence of rare inherited disorders, is the principal investigator (as stipulated by the German Drug Act) of the SELICA II trial, for which the Paul Ehrlich Institute granted approval in April 2008. Hoffmann is supported by an experienced team led by Dr. Jochen Meyburg, chief physician of the children's intensive care unit, and Dr. Martin Lindner, chief physician of the Division of Innate Metabolic Diseases. SELICA stands for "Safety and Efficacy of Liver Cell Application". The study is investigating the use of liver cell suspensions that are applied through a portal vein catheter into the liver of sick infants. These liver cell suspensions are able to replace the missing enzyme activity and prevent functional brain disorders caused by an elevated blood ammoniac concentration. The objective of the study is to help newborns suffering from urea cycle defects to survive without severe hyperammonemic crisis until the children reach the required weight to enable the transplantation of a donor liver.

The liver cell suspension used is produced by the biotechnology company Cytonet according to a proprietary, patented process in accordance with the German Drug Law. Cytonet uses liver cells removed from donor livers that cannot be transplanted. Cytonet, which is the largest cell therapy company in Germany, is sponsoring the SELICA study. The company is headquartered in Weinheim/Bergstraße and works closely with the University Hospital in Heidelberg and the Hanover Medical School. The liver cell suspensions are produced in clean room facilities according to European GMP conditions in Durham, North Carolina, USA.

Since early 2007, four children with life-threatening urea cycle defects have been successfully treated with Cytonet's liver suspension at the University Children's Hospital in Heidelberg, the Hanover Medical School and in the University Children's Hospital in Padua. (Meyburg, J. et al.: Transplantation 2009; 87, 636-641). The SELICA II study is being carried out by the Centre of Paediatrics and Youth Medicine in the new building of the Heidelberg Children's Hospital, the Hanover Medical School (Paediatric Metabolism Centre, Paediatrics II) and the University Children's Hospital at the Heinrich Heine University in Düsseldorf; there are plans to establish another study centre in Berlin.

High demands

The new University Children's Hospital building in Heidelberg (Angelika Lautenschläger Hospital) was officially opened in 2008. The construction of the new building was made possible thanks to a financial injection of 13.8 million euros from the Heidelberg patron Manfred Lautenschläger.

Liver cell transplantation places high demands not only on the quality of the suspension, but also on the hospitals and treating physicians. Prof. Hoffmann describes the requirements as follows. "For those of us who work in the field of metabolic medicine and also in the field of paediatric intensive care medicine, liver cell transplantation is one of the most difficult events that require an immediate reaction and where many processes, such as dialyses, plasmophereses, drugs, etc., must go hand in hand (see Selica II video Cytonet).

The injection of the liver cells through a portal vein catheter needs to be continuously monitored by measuring the portal vein pressure and by monitoring the flow velocity using a Doppler ultrasound device, in order to prevent portal vein thrombosis or lung embolism (this has so far only appeared in animal experiments) caused by the intrusion of liver cells into the blood circulation. In order to exclude all risks, the application of the cells needs to be constantly varied, as Dr. Meyburg explains. The physician believes that liver cell therapy has the potential to go beyond the stated objective of the SELICA II study. Meyburg reports that it was possible to measure the enzyme activities in the liver of liver cell transplant patients over a longer period of time. Exact calculations revealed that a fourfold higher enzyme activity was present 15 months after liver cell transplantation. This enzyme activity was therefore much higher than had been expected when the cells were originally applied. The foreign liver cells had not only permanently settled in the child's organ, remaining fully functional, but had also proliferated. Following the positive clinical experiences of Prof. Hoffmann's team, the physicians are optimistic that the time at which liver cell therapy is given can be systematically expanded beyond the goals of the SELICA II study and that it will soon be possible to expand the currently available therapeutic options with a therapy that has a long-term effect in newborns.

Further information
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Article

28-Jan-2010
EJ - 24.01.2010
BioRN

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