Confirmation of nitisinone efficacy for life-threatening liver disease

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A consortium of Quebec researchers coordinated by the Medical Genetics Service of the Sainte-Justine UHC has just published the findings of a 25-year study on the treatment of tyrosinemia, a life-threatening liver disease of genetic origin, which is screened at birth in the province of Quebec, where it is much more frequent than anywhere else in the world. "After five years of treatment, no trace of the disease can be detected in the liver of newborns who were treated with nitisinone starting from the first month of life," states Dr. Grant Mitchell of the Sainte-Justine UHC and the University of Montreal, who is the senior author of a study published in *Molecular Genetics and Metabolism* in September 2012.

Due to a genetic mutation, tyrosine, an amino acid found in the diet, is not properly metabolized in the liver of children with tyrosinemia. Toxic compounds can therefore build up in the liver and trigger various complications such as liver cirrhosis and liver cancer, which most often require a liver transplant to ensure patient survival. The drug nitisinone produces spectacular results, since it lowers the level of toxins by modifying the way tyrosine is metabolized. If treatment is undertaken in the first month of a child's life and complied to, impaired liver function becomes normal again.

Forty years ago, 90 % of children with tyrosinemia died before ever reaching the age of two. The study shows that today, they can enjoy normal health for at least 18 years and possibly even for the rest of their lives. In Quebec, screening at birth has been performed since 1970 and nitisinone treatment has been available since 1994. The situation is different elsewhere in the world, where in most countries neonatal screening for tyrosinemia is not available.

In fact, outside Quebec, children are diagnosed with tyrosinemia only when they show up at the hospital with severe complications, usually when they are already a few months old. For these children, the study's findings are critical. "The treatment also helps children with a late diagnosis, because it prevents acute complications, notably the need for a liver transplant," explains Dr. Mitchell.

The Quebec group's findings erase all doubt about the efficacy of nitisinone treatment and the benefits of early tyrosinemia screening. The researchers hope that their conclusions will be quickly exported and adopted so children elsewhere in the world can also benefit from this rapid and optimal treatment.

Around the world, one person in 100,000 is afflicted with tyrosinemia. In Quebec, a genetic founder effect pushes this proportion up to one person in 16,000 and even one in 1,846 in the Saguenay region. According to Dr. Guy Parizeault, the pediatrician at the Chicoutimi Health and Social Service Center (CSSS) who took over from the study's first author, Dr. Jean Larochelle, as the physician in charge of local monitoring of children with tyrosinemia, "Quebec was the ideal place to conduct this research on tyrosinemia, since there were enough patients to draw valid scientific conclusions and the province enjoys close collaboration with the physicians in charge of monitoring and the group of parents of the affected children."

Study Details

To evaluate the efficacy of nitisinone, the researchers performed a retrospective examination of the course of the disease in patients in Quebec who had not received the treatment before 1994. They then compared their observations with the results of a prospective study of the course of the disease in patients who had been screened at birth starting in 1994. All of these patients were treated with nitisinone. Physicians from all of the university centers responsible for monitoring children with tyrosinemia in Quebec took part in the collaborative study. The children were monitored locally for their

dietary and medical treatment and evaluated once a year at the Sainte-Justine UHC by a multidisciplinary team of medical specialists in genetics, liver diseases and medical imaging. The study was conducted in collaboration with patients who were members of a Quebec support group for children with tyrosinemia and their parents.

Despite the exciting conclusions, the researchers remain cautious. They stress the importance of continuing to monitor the development of complications related to tyrosinemia or the treatment itself. "We conducted this study over 25 years. It is long enough to be sure that nitisinone treatment definitely stops this liver disease or at least drastically slows down its progression," continues Dr. Mitchell. "This goes to show how some genetic diseases, even the most severe ones, are treatable," he concludes.

Provided by University of Montreal