CYSTINOSIS RESEARCH FOUNDATION

GRANT'REPORT
December 1st 2015

Project: Neurological complications in cystinosis patients

Recall:

Cystinosis is a rare autosomal recessive disease caused by intracellular cystine accumulation (1). The clinical course of cystinosis has changed from that of a largely renal disease to a multisystem disorder. In historical cohorts, distal myopathy is frequent (2, 3) and thoracic muscle weakness may impair pulmonary function. Although rare, central nervous system complications do also occur in adults with cystinosis. Two forms are observed. The first is called cystinosis encephalopathy. The other form resembles a stroke-like episode with ischemic lesions. By brain imaging, cerebral atrophy is observed in all patients with central nervous system symptoms (4), but also in patients without gross central nervous system clinical abnormality (5, 6). Calcifications may be detected. By magnetic resonance imaging (MRI), children with cystinosis evidence selective changes in cerebral white matter in areas of the dorsal visual pathway. A hypothesis is a progressive development of a microvascular disease of the brain and a cerebral cystine crystal-associated vasculopathy. However, little is known about the long-term progression of adult nephropathic cystinotic patients since cysteamine treatment became available, especially for neurological complications. Furthermore, the development of advanced neuroimaging techniques has provided new tools to investigate the underlying neurophysiopathological mechanisms of metabolic diseases. Our objective is to analyze neurological and pulmonary complications in late adolescent and adults patients with cystinosis in the era of early cysteamine treatment and their relationship with the other complications of the disease, renal function or transplantation, leukocyte cystine level, age at initiation of treatment and adhesion to treatment. Systematic neurological examination and multimodal brain MRI will be performed in a cohort of 20 cystinotic patients and compared to 20 controls presenting the same type renal dysfunction. Our hypothesis is that there is a progressive development of brain abnormalities but early treatment with cysteamine would reduce the incidence of such complications.
We began a clinical trial to evaluate this hypothesis.

General Information on the Study:

Objectives:

To analyze with modern tools the central nervous system involvement in a cohort of late adolescent and adult cystinosis patients.

Methodology

Systematic neurological examination, multimodal brain MRI and CT-scan are performed in a cohort of 20 cystinotic patients and MRI will be compared to 20 controls matched for age, sex and renal dysfunction.

Inclusion criteria:

Cystinosis patients:

- ✓ Patient aged from more than 16 years old,
- ✓ Patient with confirmed diagnosis of cystinosis,
- ✓ Patient with medical care insurance,
- ✓ Patient having dated and signed the Informed Consent Form. If necessary, the information must be given to the legal representative who can be asked to sign/co-sign the Informed Consent Form.

Controls patients:

- ✓ Patient with renal function (or dialysis/transplantation), age and sex matching with a previously included patient with cystinosis
- ✓ Patient with medical care insurance,
- ✓ Patient having dated and signed the Informed Consent Form. If necessary, the information must be given to the legal representative who can be asked to sign/co-sign the informed consent form.

Non-inclusion criteria:

- ✓ Patient presenting a contraindication to the radiologic examinations
- ✓ Patient that cannot follow the study requirements, for any geographical, social of psychological constraints.

Clinical Trial Authorization:

- French Competent Authority (Agence Nationale de Sécurité des Médicaments (ANSM)):
  Submission on April 7th 2015
  Autorisation obtained on June 2nd2015
- Ethical Committee (Comité de Protection des Personnes – IDF III):
  Submission on April 7th 2015
  Approval obtained on June 23th 2015

Patientsenrollment:

- Initiation Visit in the Clinical Service of Nephrology: September 3rd 2015
- Recruitment of the Clinical Research Technician: October 12th 2015

⇨According the availability of the 3 Tesla MRI ⇨ September 2015.

The two first patients were included and evaluated in November 19th and 26th.
Four patients are planned for the beginning of 2016.
Four other patients must be planned.

Elisabeth Hulier-Ammar, PhD
Imagine, Institute of Genetic Diseases
Head of Clinical Research

Attachment: Protocol of the study