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Familial primary distal renal tubular acidosis: Results of a multinational collaboration study

Results bear one clear key message: good treatment is important! Patients in whom the acidosis had been properly controlled by adequate treatment had better growth and better kidney function than those with inadequate treatment.

In addition to regulating the body's fluid balance, by excreting greater or smaller amounts of urine, the kidneys also maintain the proper balance of electrolytes (salts) and the pH (an acid-base equilibrium) within our body. Excess acid is secreted into the urine by healthy kidneys. This process takes place in a specific part of the kidney ('distal tubules'). When this excretion of acid is disturbed, the concentration of acid in the body increases, a disorder called distal renal tubular acidosis (dRTA). "Too much acid in our bodies has a lot of negative effects", explains Prof. Dr. Detlef Bockenhauer, London. 'In the first instance, the acid dissolves the bones, leading to complications, such as rickets. And the calcium released from the bone ends up in the urine, where it can cause kidney stones.'

Distal renal tubular acidosis is a rare disease (it affects only about 1:100.000 people) and is congenital in most cases (also called familial or primary dRTA). Mutations in six genes have been identified, which can cause the disorder. Symptoms may include large volumes of urine, thirst, fatigue, growth disorders and failure to thrive, bone damage (similar to rickets or osteoporosis) or kidney stones. Recurrent kidney stones or severe calcification of kidney tissue (nephrocalcinosis) may lead to progressive chronic kidney disease. A marked deficiency of serum potassium can be another complication, which can lead to paralysis, cardiac arrhythmia and, ultimately, death. Some inherited forms also lead to progressive deafness. Symptoms may vary considerably for the various gene mutations, with some patients remaining asymptomatic and the diagnosis is made only incidentally.

Treatment involves patients having to take alkali supplements (acid binders such as bicarbonate or citrate) on a daily basis for the rest of their lives.

"Because the disease is so rare, there are no major long-term studies of its progression and prognosis, which makes it more difficult to manage it medically and to properly

inform parents and patients", explains Prof. Bockenhauer. For these reasons, the aim of a multinational initiative launched as part of ERKNet (the European Reference Network for Rare Kidney Diseases), in cooperation with the Working Group on Inherited Kidney Disorders (WGIKD) of the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) and the Inherited Renal Disorders Working Group of the European Society for Paediatric Nephrology (ESPN), was to clarify a number of unresolved questions in order to improve the diagnosis, therapy and handling of the disease for physicians, patients and parents. Paediatric and adult nephrologists were contacted for the study [1], and all available data (demographic, biochemical, genetic and clinical) were collected using online forms.

The results of the study have now been released. Data on 340 patients from 29 countries were collected (52% female). The median age of patients was 11 years (0-70), 83 patients (24%) were adults (≥18 years). The median presentation age was 0.5 years (range 0–54) and 11 years at last follow-up (0-70). Mutation analyses were performed in 206 of the patients (61%); gene mutations were identified in 170 of that group (83%). The adult patients had reached heights slightly below average (with a standard deviation score (SDS) of -0.57). The prevalence of stage 2 chronic kidney disease (CKD) was 35% among children and 82% among adults. Calcification of kidney tissue (nephrocalcinosis) was reported in 88% of patients. Kidney stones (nephrolithiasis) were most common in cases with SLC4A1 mutations (42% vs. 21%). 36% had hearing loss (most frequently in cases with ATP6V1B1 mutations). Adequate therapy with a normal acid-base balance and without excess urinary calcium loss was achieved in only 158 patients (51%) – predominantly in countries with a high gross domestic product. Importantly, when analysing the data from adult patients, the researchers noted that those with adequate treatment had a better final height and better kidney function, compared to those, in whom adequate buffering of acid was not achieved. "This is an important message to all clinicians taking care of these patients: we really must make sure to control the disease as effectively as possible so that our patients can reach their full growth potential and maintain overall kidney function!"

"All in all, the progression and outcome of distal renal tubular acidosis in this large cohort of patients can be considered favourable", Prof. Bockenhauer summarises. "Most patients reach an adult height in the normal range, and no patient had severe chronic kidney disease (stage 5 CKD) or needed dialysis. Nevertheless – 82% of the patients reached stage 2-4 CKD; this is likely attributable to the fact that optimal management of acid-base balance was achieved in only about half the patients. Future efforts must now concentrate

on establishing the best possible management of treatment for all patients in all countries."

[1] Lopez-Garcia SC, Emma F, Walsh SB et al. Treatment and long-term outcome in primary distal Renal Tubular Acidosis. Nephrology Dialysis Transplantation 2019; https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfy409/5327293

About ERA-EDTA

With more than 11,000 members, the ERA-EDTA ("European Renal Association – European Dialysis and Transplant Association") is one of the biggest nephrology associations worldwide and one of the most important and prestigious European Medical Associations. It supports basic and clinical research in the fields of clinical nephrology, dialysis, renal transplantation and related subjects. It also supports a number of studies as well as research groups and has founded a special "Fellowship Programme" for young investigators as well as grant programmes. In order to involve young nephrologists in all its activities, ERA-EDTA has created the "Young Nephrologists' Platform" (YNP), a very active committee whose board includes members who are 40 years old or younger. In addition, it has established various working groups to promote the collaboration of nephrologists with other medical disciplines (e.g. cardiology, immunology). Furthermore, a "European Renal Best Practice" (ERBP) advisory board was established by the ERA-EDTA to draw up and publish guidelines and position statements. Another important goal of the ERA-EDTA is education: The series of CME courses combined with the annual congress offer an attractive scientific programme to cover the need for continuous medical education for doctors working in the fields of nephrology, dialysis and transplantation. The association's journals, NDT (Nephrology, Dialysis, Transplantation) and CKJ (Clinical Kidney Journal), are currently the leading nephrology journals in Europe; furthermore NDT-Educational is the Society's online educational journal , with free access for all users, as well as being a very important and useful feature of the NDT-Educational "Literature Review". The ERA-EDTA Registry is a large epidemiologic database comparing countries by assessing nephrology practices throughout Europe. ENP, the European Nephrology Portal, is the latest new initiative of ERA-EDTA, where all those interested in the activities of the Society can find everything that is happening, all in one place. Finally, ERA-EDTA is a member of the European Kidney Health Alliance (EKHA), a consortium of patients, nurses and foundations relating to renal issues that actively interacts with the European Parliament. For more information, please visit www.era-edta.org