Urea Cycle Disorders

The Urea Cycle Disorders are a group of genetic disorders caused by a deficiency of one of the six enzymes in the urea cycle that is responsible for the removal of ammonia from the blood stream. When the body digests protein it is broken down into small molecules known as amino acids. These travel through the blood stream and are transported to the cells. Excess amounts of these amino acids are converted into a toxic substance known as ammonia. Once the ammonia is in the liver, the ammonia is converted to urea and excreted in the urine. In urea cycle disorders one of the six enzymes does not function properly and ammonia is not removed from the blood stream.

There are six urea cycle disorders:
- Arginase Deficiency (AG)
- Argininosuccinic Aciduria (ASA)
- Carbamyl Phosphate Synthetase Deficiency (CPS)
- Citrullinaemia
- N-Acetylglutamate Synthetase Deficiency (NAGS)
- Ornithine Transcarbamylase Deficiency (OTC)

The Urea Cycle Disorders are usually inherited from the genes of the parents by a method called autosomal recessive inheritance. This is when a child inherits a gene for the disease from both parents. If a child receives one normal gene and one gene with the disease, the child will be a carrier for the disease and usually does not show any symptoms. The risk of transmitting the disease from a couple who are both carriers is 25%, there is a 50% chance that their child will be a carrier and there is a 25% chance that the child would be genetically normal. This risk is the same for each pregnancy. Ornithine Transcarbamylase Deficiency is inherited by a method called X-linked inheritance. This is when the diseases are coded on the X-chromosomes of genes. Females have two X chromosomes and any disease traits that are on one of the X chromosomes is usually masked by the other normal X chromosome. Males have one X and one Y chromosome, because there is only one X chromosome the disease is usually expressed and therefore male children will have the disease. It should be noted that some female carriers do have symptoms. These are general descriptions of the methods of inheritance, for further information a genetic counselling service should be consulted.

Symptoms may occur either in the neonatal period, during childhood or during adolescence or adulthood. In the neonatal period, babies usually present with symptoms after the first 24 hours of life. Symptoms include irritability, drowsiness, rapid breathing, poor feeding, vomiting and an enlarged liver. This progresses to seizures, low muscle tone (hypotonia), respiratory distress and in some cases, coma and death if they are not treated. The acute neonatal symptoms are most frequently seen in boys with Ornithine Transcarbamylase Deficiency. Symptoms that present during childhood may include hyperactive behaviour and
in some cases self-harming behaviour, screaming, an enlarged liver and avoidance of meat or other high-protein foods. Individuals may experience vomiting and may become lethargic and delirious especially after high-protein foods. If untreated, this can lead to coma and death. Episodes of high levels of ammonia in the blood (hyperammonia) can be caused by high-protein foods, viral illness and exhaustion. In the adolescence/adulthood onset, individuals may be lethargic, delirious and exhibit stroke-like episodes. Symptoms usually occur after viral illness, childbirth and the use of anti-epileptic drugs known as valproic acid. Individuals are at high risk of permanent damage to the brain, coma and death if they are undiagnosed and untreated.

The childhood form of this disorder can be misdiagnosed as Reye’s Syndrome. Treatment of an acute episode includes restricting any further intake of protein to prevent any additional increase in ammonia levels.

The optimal aim of managing Urea Cycle Disorders is to manage and maintain “safe” levels of ammonia in the blood, help to promote the removal of ammonia from the body through alternative pathways and prevent any increase which can be toxic. A low-protein diet will need to be followed and will be put in place by a specialist dietitian. A carefully balanced diet is necessary to ensure that the body receives adequate calories and essential amino acids. Vitamin supplements may be recommended. Dietary protein must be carefully monitored and some protein restriction is necessary. However, if the diet is restricted too much it can also be harmful. Therefore, any dietary changes must be made by a specialist dietitian who will aim to maintain the correct nutritional balance for each individual in each stage of growth, as this is critical in avoiding hyperammonemic crises. Specialist dietary supplements are available in formulas which are produced especially for Urea Cycle Disorders to help ensure the correct level of protein is maintained.

Sodium phenylbutyrate (Ammonaps/Buphenyl) is the main medication that is currently used in the management of Urea Cycle Disorders. Sodium benzoate is also used in some patients, either taken on its own or used with Ammonaps. Both of these medications help to prevent high ammonia levels in the blood (hyperammonaemia). L-citrulline (for use in OTC or CPS Deficiency) or L-arginine (for use in Argininosuccinic Aciduria or Citrullinamia) may also be required. However, these are not to be used in Arginase Deficiency. These supplements help in the removal of ammonia from the body. Antacids are sometimes prescribed to counteract any gastrointestinal side effects of drug treatment such as reflux or stomach aches. If feeding problems are present a gastrostomy tube (a tube surgically implanted in the stomach) or a nasogastric tube (manually inserted through the nose into the stomach) may be recommended. Frequent blood tests are required to monitor the condition. Liver transplants have been used in the treatment of this condition but have to be carefully considered and are only available if other treatment options have failed.

In the case of a hyperammonaemic crisis, individuals are treated with an emergency regime when they are unwell and/or unable to tolerate a normal diet, this is usually given as a high glucose energy drink such as Maxijul. The emergency regimen is prescribed to suit the individual. If the individual continues to vomit and appears not to be recovering, it is necessary to contact the doctor or take them to casualty. If this happens, a glucose solution is given directly through the vein; medications (sodium phenylbutyrate and sodium benzoate) may be used and in some cases Arginine. If this does not appear to be working dialysis may be needed to help reduce levels of ammonia.
This information is fully sourced and referenced, for more detailed information and references please contact CLIMB by email, letter or telephone.

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