Aminoacidurias

The term aminoaciduria is applied when more than 5% of the filtered load is detected in the urine.\(^1\) It may result from an inherited metabolic abnormality, in which case the aminoaciduria is a permanent finding, or it may be an acquired abnormality which may either be transient or become permanent.

### Classification

Three distinct groups of inherited aminoacidurias are distinguished, based on the net charge of the target amino acids at neutral pH:\(^2\)

- Acidic (negative charge)
- Basic (positive charge)
- Neutral (no charge)

Transient aminoacidurias may occur during the diuretic phase after acute renal insufficiency, or as a result of a deficiency of potassium.

Aminoacidurias of longer duration occur as a result of poisoning with heavy metals, particularly cadmium and uranium, but also with lead or mercury.

There is aminoaciduria found in patients with Wilson's disease; it is associated with the toxic effect of copper on the renal tubule, which characteristically accumulates in patients with this disease.

### Pathogenesis

- Under normal circumstances, the renal tubules reabsorb in excess of 93% of the amino acids filtered from the plasma, influenced by the glomerular filtration rate. When the filtered load of amino acids is increased, there is an increase in both the amounts reabsorbed and those excreted. However, the ability of the renal tubule to respond to an increased filtered load of amino acids is so great that a maximum rate of reabsorption has not been found in the human.
- In some instances, the aminoaciduria is generalised; there is increased excretion of all of the amino acids occurring in the plasma. In other instances, the aminoaciduria is more specific, in that there are increased amounts of some amino acids in the urine while all others are excreted in normal amounts.
- Secondary or ‘overflow’ aminoaciduria can also be seen in conditions in which there is hyperaminoacidaemia.

Some important aminoacidurias are described below but phenylketonuria, homocystinuria, maple syrup disease and other inborn errors of metabolism are mentioned in detail in separate articles.

### Fanconi's syndrome

Fanconi's syndrome is the most frequently studied inherited aminoaciduria. The syndrome is characterised by a generalised aminoaciduria and by other renal tubular defects affecting reabsorption of phosphate and glucose. Frequently, the renal handling of potassium and water, as well as the secretion of hydrogen ions and the manufacture of ammonia, are also affected. The aminoaciduria itself, although generalised, is minimal and of no metabolic consequence.

### Cystinuria

In this condition, the glomerulus fails to resorb cystine, ornithine, lysine and arginine into the tubule and they are excreted into the urine.

There are three types of cystinuria, distinguished by the mode of inheritance and by the pattern of the tubular amino-acid transport.\(^3\) Cystinuria is an autosomal recessive disorder which affects approximately 1 in 7,000 people.\(^4\) The rBAT gene which controls cystine excretion was isolated in 1992.\(^5,6\)

### Presentation

It usually presents with cystine stone formation in the kidneys; a quarter of patients experience symptoms in the first decade of life. There may be pain, haematuria, renal obstruction and infection. Renal failure can sometimes occur.\(^7\)

### Diagnosis
Calculi are frequently multiple and bilateral and often form staghorns. The diagnosis is suspected when stone analysis reveals a cystine stone. Cystine stones are pale yellow. Diagnosis can be confirmed by an amino-acid chromatogram and quantification of cystine excretion. This is worth doing even when the stone is mainly composed of calcium, which can occur in cystinuria due to predisposing infection.

**Management**

For a patient with cystinuria who does not have a stone, first-line therapy in most cases is a conservative approach. This includes:

- Large-volume fluid intake (at least 3 litres/day in adults) - this must include 500 ml before retiring to bed, with a nocturnal rise to pass urine and drink a further 500 ml. Keeping the urine dilute over the 24-hour period is the difficult part, but may be sufficient treatment for those without stones.
- Regular urine pH monitoring (urine pH level of 7.5 and <8).
- Dietary restrictions - reduced protein intake diminishes cystine excretion, but this is not often used in treatment.
- Urinary alkalinisation with potassium citrate - cystine is much more soluble at alkaline pH (>7.5). Use of sodium bicarbonate is limited by the large doses (6 g/day or more) needed to raise urine pH significantly. These are contra-indicated in hypertension or renal failure. In addition, alkaline urine may predispose to the precipitation of calcium salts.

If this standard therapy fails to achieve the urinary cystine concentration of 300 mg/L, then medical therapy with d-penicillamine, alphamercaptopropionylglycine (alpha-MPG), or captopril must be added.

Alternatives include sulphhydryl compounds, eg mercaptopropionylglycine, which have been used in some countries, but are not available in the UK. Captopril is a sulphhydryl compound which forms a disulphide with cystine. Reports of decreased cystine excretion related to treatment with captopril have not been confirmed and no therapeutic use has yet been established.

Patients with stone disease should be treated according to the location and size of the stone. Cystine stones are not easily broken by lithotripsy.

Percutaneous removal may have its place for smaller stones, particularly in those who cannot take penicillamine and who are unable to regulate their drinking adequately. Keeping patients free from stones, using minimally invasive techniques, helps to reduce the incidence of stone recurrence.

**Glycinuria**

This is a rare autosomal recessive neutral aminoaciduria. It is a clinically benign disorder where the defective protein has not yet been identified. There is no defect in reabsorption of other amino acids. The renal tubular defect produces renal oxalate stones.

Glycinuria has been described more often in the Ashkenazi Jewish population.

Glycine shares its renal tubular reabsorption mechanism with the imino acids (proline and hydroxyproline). Iminoglycinuria is also a benign inborn error of amino acid transport and a normal finding in neonates and infants under 6 months of age.

**Hartnup disease**

Hartnup (H) disease is a rare autosomal recessive metabolic disorder (1 in 14,000 in the USA) where renal tubular transport is defective and causes gross aminoaciduria. Tryptophan and other neutral amino acids are not absorbed in the small intestine and are converted by gut bacteria into indolic compounds that are toxic to the CNS. The renal loss of amino acids plus poor absorption from the gut cause protein malnutrition. Abnormal tryptophan transport leads to niacin deficiency, or pellagra.

**Genetics**

The mutated gene (SLC6A19) is located on chromosome locus 5p.15.33 and is known to encode an abnormal neutral amino-acid transporter. Other mutations have been described and this may explain, at least in part, the clinical heterogenicity. Heterozygotes have no abnormality. Differing mutations may be associated with different phenotypic expression.

**Presentation**

There is a wide clinical spectrum but most patients are asymptomatic. Symptoms are often intermittent with exacerbations provoked by:

- Change of season - northern hemisphere spring/summer with increasing sunlight.
- Febrile illness.
- Poor nutrition.
- Increased physical activity.
- Sulfonamides.
Symptoms tend to arise between the ages of 3-9 years, although sometimes in infancy. It occasionally presents in adults. Episodes of neurological and dermatological problems progress for several days and last from a week to a month before spontaneous remission. Skin problems usually precede neurological features. Psychiatric symptoms including anxiety, emotional instability and changes of mood are common. Psychosis and delirium are rare.

Photosensitivity occurs and the skin becomes red after exposure to sunlight. Continuing exposure leads to dry, scaly, well-delineated eruptions, sometimes resembling chronic eczema. These eruptions tend to affect the forehead, cheeks, peri orbital regions, the dorsum of the hands, and other light-exposed areas. Lesions on the face may be similar to the butterfly rash of systemic lupus erythematosus. Skin changes cause permanent hypopigmentation and/or hyperpigmentation, made worse by further exposure to sunlight.

Mental development is usually normal, but mild learning difficulties (IQ 50-70) are described in a few patients. Neurological symptoms may vary and are fully reversible. They include:

- Intermittent cerebellar ataxia.
- Wide-based gait.
- Spasticity.
- Delayed motor development.
- Tremor.
- Headaches.
- Hypotonia.

Ocular manifestations include diplopia, nystagmus, photophobia, and strabismus. Gingivitis, stomatitis and glossitis suggest niacin deficiency. Diarrhoea occasionally precedes or follows attacks of the disease. Short stature has been described but is not marked.

**Investigations**

Urine chromatography shows increased levels of neutral amino acids. Urinary 5-hydroxyindoleacetic acid may be found after an oral tryptophan load. Urine excretion of proline, hydroxyproline, and arginine is normal. Skin biopsy may, rarely, be required.

**Management**

General measures include a high-protein diet, avoidance of sunlight, use of sun protection and neurological and psychiatric treatment where there is CNS involvement. Nicotinic acid or nicotinamide at 50 mg to 300 mg daily can provide remission from both the skin and neurological manifestations. Maternal Hartnup disease does not have an adverse effect on the fetus.

**Complications**

Severe CNS involvement may, rarely, be fatal in the first years of life. Psychotic episodes and delirium occur in a few patients. Mild mental retardation is uncommon. Permanent hypopigmentation and/or hyperpigmentation of the skin occur with repeated exposure to sunlight.

**Prognosis**

Malnutrition and a low-protein diet increase morbidity. Attacks become less frequent with increasing age.

**Lysinuric protein intolerance**

This is a relatively rare autosomal recessive disease causing a defect in diamino acid transport. There have been approximately 100 reported cases, mainly in Finland. There is defective ornithine, lysine and arginine transport affecting the renal tubule and intestine with only minor defects of cystine transport. It is characterised chemically by renal hyperdibasic aminoaciduria and by impaired formation of urea with hyperammonaemia after protein ingestion. Approximately 50 different mutations have been identified in the SLC7A7 gene but no genotype-phenotype correlation has been established.

**Presentation**

Patients thrive during breast-feeding but ingestion of cows’ milk causes diarrhoea and vomiting. Failure to thrive and poor appetite are common with poor growth. Stones do not form. Occasionally, intermittent hyperammonaemic encephalopathy occurs. Osteoporosis is an important part of the clinical picture, with vertebral collapse.

Diagnosis depends upon the demonstration of a failure to increase plasma lysine levels after oral lysine loads or the ingestion of lysyl peptides.

**Management**

General measures include advising the patient to avoid complete protein abstinence for longer than 24-48 hours. Varicella immunisation is advisable in those without previous history of chickenpox or varicella zoster and those exposed should be treated as immune-compromised persons.

Long-term management includes dietary protein restriction, oral supplementation with citrulline and nitrogen scavenger drugs, low-dose lysine and carnitine:

- Symptoms can be largely prevented by a low-protein diet. However, adequate calorie intake is difficult to sustain in infancy and appetite often remains poor.
Protein restriction does not correct lysine deficiency. Long-term low-dose oral lysine supplementation has been found to be beneficial and well-tolerated.\(^{[23]}\)

Oral citrulline (2.5 to 8.5 g/day) absorbed via a different transport system, corrects ornithine and arginine deficiency and lowers plasma ammonia by priming the urea cycle.\(^{[26]}\) Citrulline treatment should be maintained but intravenous citrulline is not readily available.

During acute hyperammonaemic crises:\(^{[27]}\)

- Arginine chloride and nitrogen scavenger drugs (sodium benzoate, sodium phenylacetate) to block ammonia production.
- Reduction of excess nitrogen in the diet.
- Providing energy as carbohydrates to reduce catabolism.

**Complications**

Pulmonary alveolar proteinosis and renal disease (progressive glomerular and proximal tubular disease) are observed increasingly often in this condition.\(^{[23]}\)

**Further reading & references**

- Guay-Woodford LM; The Kidney Atlas. Chapter 12. Renal Tubular Disorders
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- Lysinuric Protein Intolerance
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