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A REVIEW OF OXALOSIS

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Abstract

Oxalosis is an inborn error of metabolism, with autosomal recessive transmission, defined by an excessive endogenous production of oxalic acid, with secondary deposits in different tissues (eyes, bones, muscles, blood vessels, heart and other organs) and a high renal excretion. Hyperoxaluria is rare, though it can be identified in about 20 % of individuals with kidney stones. Its quick diagnosis and treatment are essential to the long-term health of kidneys. The aim of this article was to make a review of the literature regarding this potentially lethal condition.

key words: *oxalosis, hyperoxaluria, food, kidney disease*

Etiopathogenesis

The biochemical disturbance which leads to an abnormal high production of oxalic acid is not fully known, but seems to be intimately related to the metabolism of glycine. It seems there are two enzymatic deficiencies involved, each of them channeling the conversion of glyoxylic acid (derived from glycolic acid) to oxalic acid.

In the case of a reduced activity of glyoxylate transaminase (the most frequent form), the glyoxylic acid cannot be converted to glycine by transamination. Through these means, the alleged glycolic aciduria or type 1 hyperoxaluria is produced, a disorder defined by high renal excretion of oxalic acid, glycolic acid and calcium oxalate [1,2].

In the case of the second enzymatic deficiency, we observe a reduced activity of glyoxylate reductase, which impairs the reconversion of glyoxylic acid to glycolic acid. Through these means we encounter the L-glyceric aciduria (the accumulated hydroxyl-pyruvate is reduced to L-glyceric acid by lactate dehydrogenase) or type 2 hyperoxaluria [2,3].

Irrespective of the nature of the enzymatic deficiency, the biochemical consequence is represented by the accumulation of glyoxylic acid which converts to oxalic acid. The last mentioned, in its turn, should be metabolized and must be excreted. It is partially eliminated through the kidneys, where, due to its high concentrations, it progressively induces nephrolithiasis and nephrocalcinosis. The renal impairment is constant and the renal tubes are filled with oxalate crystals. These crystals are located in the interstitial tissue, where they lead, in the long run, to the settlement of a sclerotic reaction, with cellular infiltrate in the proximity of these deposits.

Another part of the oxalic production diffuses in the tissues, where it induces local morphofunctional alterations due to excessive precipitation (hepatic, pancreatic, parathyroid,

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suprarenal glands, hypophysis, thymic, splenic, vascular, cartilaginous, bone, cardiac) [1-3].

Clinical and Laboratory Diagnosis

The disease may occur precociously, beginning with the first months of life, or later on. The sooner the onset of symptoms, the more rapidly the illness progresses, the patients eventually dying due to end stage kidney disease. In the case of later onset, the illness progresses slowly and the patients are able to survive up to the age of 50-60 years.

In the typical cases, the symptomatology develops when the oxalic lithiasis is established. As a general rule, the calculi are bilateral, relapsing, inflicting lumbar pain, nausea and vomiting, anxiety, frequent and painful urinary disturbances. In the long run, signs of renal insufficiency associate. The presence of oxalic lithiasis in children or young adults, particularly when there is a family medical history of nephrolithiasis, leads with great probability to the diagnosis of oxalosis.

Renal lithiasis can lack, and in these cases, the diagnosis is established with greater difficulty. In this case, the disease presents itself as a progressive renal insufficiency, associated with proteinuria and often urinary tract infections. The diagnosis of oxalosis is suggested by the evolution, the presence of family medical history and the existence of various visceral involvements (for example – the occurrence of atrioventricular conduction disturbances, due to the infiltration of myocardium with oxalate crystals). Occasionally, the patients become feverish due to urinary tract infections enhanced by the oxalic tubular and lower urinary tract obstruction. The kidneys are not enlarged, although there is a certain degree of hydronephrosis. The blood pressure initially records normal values, later it inconstantly increases.

Some patients present inflammatory articular symptoms due to the local deposits of oxalate. Sometimes, these are clinically comparable with the ones encountered in gout. This is the reason why some authors proposed the name of "oxalic gout". It is associated with migraine, epigastric pain, mucomembranous enterocolitis, low blood pressure and asthenia. In children, oxalosis is accompanied by bone anomalies and growth disturbances, disclosed by delayed stature-ponderal development. In adults with an adequate development, a certain degree of osteopathy is though often identified, defined as bone lysis and metastatic calcifications, signs which plead for osteodystrophy in a secondary hyperparathyroidism, along with a fibro-osteoclastic reaction observed on histological examination [4,5].

Apart from the signs already presented, a series of disturbances have been observed, and their correlation with the rising level of oxalate is not fully accepted. Among these, we mention: nervous disturbances (depression, psychosis, anxiety, hypochondriac symptoms, migraines, sciatic neuritis, intercostal neuralgia, epileptiform seizures – the last ones were mentioned in patients with oxalate crystals in the cerebrospinal fluid), digestive disturbances (dyspepsia, gastroduodenitis, mucomembranous enterocolitis, constipation) and respiratory disturbances (asthma attacks) [4].

The laboratory data confirm the clinical presumption of oxalosis. For this purpose, we measure oxaluria, urinary glycolic acid, oxalemia, calcium levels in blood, uricemia, urinalysis, urine culture, radiological examination of kidneys and optionally, kidney biopsy.

Oxaluria (normal range = 10 – 30 mg/day) reaches values of 100 – 400 mg/day in oxalosis. The daily fluctuations are considerable, so repeated measuring is required. In addition, the

occurrence of renal insufficiency decreases the value of oxaluria. Oxaluria is not specific for oxalosis; hyperoxaluria is encountered in various pathological states, such as gout, hepatic and biliary impairment, diabetes mellitus, sarcoidosis and heart failure. However, the detection of hyperoxaluria outside other clinical manifestations allows the early diagnosis of latent forms in the families of patients with oxalosis.

Regarding oxalemia, it is rarely measured, due to the absence of accurate measuring methods. Its normal value is below 0.8 mg/dl. A higher value of oxalemia is observed in respiratory and hepatic diseases, decompensated heart failure, diabetic coma. Furthermore, hyperoxalemia exacerbates as renal failure advances.

Calcemia is generally high. We also observe high values of uricemia, present in a quarter of patients with oxalosis. Hyperuricemia could probably be due to the increased concentration of organic acids such as oxalic acid and glyoxylic acid in the tubular renal cells, as they interfere with the tubular secretion of urates, using a competitive mechanism. In type 2 hyperoxaluria, we encounter high L-glyceric aciduria. It is used as a differential criterion from type 1 hyperoxaluria, where high quantities of glycolic acid are excreted through urine.

The abdominal X-ray highlights the presence of renal calculi (calcium oxalate lithiasis is radiopaque) or nephrocalcinosis (calcium deposits in kidneys) [5].

Urinalysis shows the presence of oxalates, frequent leukocytes, red cells, albuminuria and often bacterial flora. The urine culture shows the presence or the absence of urinary tract infections [6].

Dietary Treatment

In oxalosis, diet has a limited efficiency. It aims at the restriction of consumption of foods rich in oxalic acid. It should also limit the intake of foods rich in calcium, salt and ascorbic acid, reduce the lipids and avoid the abuse of carbohydrates. At the same time, increased intake of products rich in phosphates, pyridoxine and magnesium is recommended [7].

The restriction of intake of foods rich in oxalic acid should be implemented according to the information given in Table 1.

Table 1. The content of oxalic acid in main foods (mg/dl). (Adapted after [7,8])

Foods with high content of oxalic acid	Cocoa	1000
	Spinach	890
	Watercress	835
	Tea	800
	Pepper	660
	Celery	720
	Rhubarb	500
	Dark chocolate	350
	Beetroot	338
Foods with moderate content of oxalic acid	Figs	200
	Parsley	190
	Cranberries	88
	Milk chocolate	60
	Celery leaves	50
	Dry plums	40
Foods with low content of oxalic acid	Carrots	33
	Green beans	31
	Endives	27
	Oranges	24
	Onion	23
	Strawberries, blackberries	18
	Blueberries, apricots	14
	Green plums	10
	Tomatoes	7.5
	Cabbage	7.4
	Bananas, pineapple	6.4
	Brussels sprouts	5.9
	Potatoes	5.7
	Asparagus	5.2
	Pears	3
	Dry apricots, peaches, wine	traces
Foods with no content of oxalic acid	Meat, fish Cheeses, milk Eggs Fats Cereals, pasta Sugar Cucumbers, radishes, cauliflower, peas Grapefruit, melons, grapes, apples Cherries, fruit juice	

Generally, we must take into account the fact that the main foods rich in oxalic acid are vegetal products, except for apples, lemons, grapefruits, cucumbers, cauliflower, peas, radishes, which have no content of oxalic acid.

The foods rich in oxalic acid (cocoa, spinach, watercress, tea, celery, rhubarb, dark chocolate, beetroot) should be excluded from the diet. Those with medium content of oxalic acid should only have a limited intake. We should also limit the foods which generate oxalic acid by decomposition, although their oxalic acid content is not high. They release high quantities of oxalic acid by gut fermentation, which is afterwards assimilated through intestinal mucosa. The foods included in this category are potatoes, legumes, concentrated sweets and pasta. As a matter of fact, foods rich in carbohydrates promote the production of oxalic acid. This is the reason why some authors advise a low intake of carbohydrates [7].

The intake of lipids should be also decreased since the non-absorbable fatty acids generate insoluble calcium complexes in the intestinal lumen, thus preventing the formation of insoluble and non-absorbable calcium oxalate precipitates. Secondly, some fatty acids can increase the permeability of colon mucosa for oxalates, favoring their reabsorbtion from the bowel.

Because the oxalates deposit in the tissues as calcium oxalate microcrystals, calcium intake should be limited up to 600 mg/day. Although, theoretically, increased intake of calcium might block the absorption of a part of the intestinal oxalates, bearing in mind that in oxalosis the excess of oxalate is endogenous, the presence of high quantities of alimentary calcium could enhance formation of tissue deposits of oxalates [8].

Simultaneously with the restrictions mentioned above, the high intake of ascorbic acid should be avoided as it is a predecessor for oxalate production. The dietary limitation is hard to achieve, as a large proportion of vegetables and fruits with low or no content of oxalic acid also have high content in vitamin C (ex. cauliflower, Brussels sprouts, grapefruits, asparagus, and oranges).

Salt restriction is used in the diet of oxalosis patients as it partakes in the decrease of calciuria and thus the possibilities of renal or urinary tract deposits of oxalates. The canned and salty foods are forbidden. Foods are cooked without using salt [7,9].

In oxalosis, the restriction of protein was also experimented, with the aim to limit as much as possible the glycine intake. The therapeutic results were minimal and temporary.

The administration of supplementary pyridoxine was also attempted (200 – 400 mg/day). It is sometimes useful in the glyoxylate transaminase deficiency (the coenzyme of this enzyme is vitamin B6). Some therapeutic effects were acquired in some cases, by using diets rich in phosphates. It looks as if the supplementary phosphates decrease the renal calculi formation. The diet must also have an adequate content of magnesium.

In parallel to the dietary steps mentioned above, we must also ensure an increased diuresis, attained by the daily intake of over 2000 ml of fluids. This can be associated with thiazide diuretics (calciuria decreases at the same time, thus reducing the possibility of calcium oxalate crystals formation).

The achievement of an increased diuresis diminishes the degree of supersaturation of urinary crystalloids, thus limiting the aggregation process – the start point for the renal lithiasis. Furthermore, the possible deposits of urinary crystalloids are carried along with the urinary flux and eliminated from the body. The higher the urinary volume, the higher the

capacity of dilution for mineral salts is. We must emphasize that an increased diuresis is indicated in patients with urinary lithiasis only in the absence of renal colic, and in patients with incomplete mechanical obstacles. Otherwise, there is the possibility of sudden distension of urinary tract above the obstacle by forcing the diuresis, thus favoring the renal colic.

Besides the prevention of calculi formation, the diuresis therapy is used to excrete certain urinary concretions. Overall, we assess that a calculus lower than 1 cm in length has real chances to be excreted through the urinary flux. The size of the calculi is measured using X-ray and ultrasound methods.

Alongside with the effect of mechanical removal of renal calculi, at the same time, increased diuresis prevents the increase in size of already existing calcium oxalate concretions, the superinfection of the lithiasis and it enables the healing processes of lesions in the urinary tract mucosa.

The increased water intake is also an useful therapeutic action against urinary tract infections, acquired by multiple mechanisms. Firstly, an abundant diuresis carries off a large amount of bacteria located in the urinary tract. The wash out effect is accompanied by a decrease in the number of bacteria, and their harmfulness is thus diminished. Secondly, the attainment of a frequent and abundant urinary flux impairs the ascent of bacteria towards the upper urinary tract, thus protecting the kidneys. Some studies suggest that the ascent of bacteria is not performed if the urinary flux is higher than 25 ml/hour (600 ml/day). In the diuresis diet, the urinary flux exceeds 100 ml/hour (2400 ml/day).

We noticed that the watery diuresis has an important therapeutic role when associated with antibiotherapy. The antibiotic doses are still very efficient in the diluted urine.

Another advantage of increased water intake in urinary tract infections is the prevention of increase of medullary interstitium hypertonicity [10]. It is a vulnerability factor for infections, as it decreases the capacity of leucocytes to travel to and remove the bacteria. At the same time, we limit the efficiency of other antimicrobial mechanisms, such as the reaction between antibodies and the microbial capsule, and the decrease of activity of the complement. By increasing diuresis, we reduce the renal interstitium hypertonicity, thus enabling the action of leukocytes and activate both the complement factor and the reaction of antibodies against bacteria. The decrease of medullary interstitium hypertonicity hinders the development of resistant bacteria [11].

We noticed that the abundant diuresis also limits the microbial influence over the process of mineral salt precipitation, thus decreasing the lithogenic risk.

The increase of diuresis is considered as a nonspecific therapeutic method, really useful in reducing the risk for calcium oxalate concretions formation, of their urinary excretion and of urinary tract infections [11-13].

For the diuretic diet to achieve its maximum effect, we should prescribe 6 to 8 intakes of water, 400-500 ml each (5 to 6 intakes during the day and one at bedtime).

Conclusions

Oxalosis will become progressively more severe as long as the blood oxalate concentration remains high, and can lead to severe organ involvement and in the end death. For this reason, prompt diagnosis and treatment are essential.

Dialysis can remove extra oxalate from the blood, but in most patients with primary hyperoxaluria, dialysis cannot keep pace with the large amount of oxalate produced by the

liver. As a consequence, a kidney transplant or kidney-liver transplant may become necessary. Future research may help us to better understand the cause of the high urine oxalate in these patients.

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