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RESEARCH ARTICLE

PRIMARY HYPEROXALURIA TYPE I: FROM INFANTILE TO ADULT FORM WITH END-STAGE RENAL FAILURE: RARE CASE AND THERAPEUTIC ASPECTS

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Abstract

Primary hyperoxaluria type I (HP1) is a very rare autosomal recessive inherited metabolic disease due to a hepatic alanine-glyoxylate aminotransferase (AGXT) enzyme deficiency. The result is excessive production and elimination of oxalate and glycolate leading to renal failure and systemic thesaurismosis. Diagnosis is based on oxaluria, followed by genotyping, as confirmation of the type of hyperoxaluria is essential for management and allows prenatal diagnosis. Conservative treatment (pyridoxine, hydration, crystallization inhibitors) is essential and must be early and the surgical management of recurrent calculi is very difficult, and requires the least invasive procedures possibleby experienced urologists in order to preserve as much renal parenchyma as possible. It is a serious disease that is often diagnosed late and its radical treatment requires costly and demanding hepato-renal replacement. Knowledge of thealanine-glyoxylate aminotransferase gene and genetic progress has made its prevention possible through prenatal diagnosis and genetic counseling. In this article, we present the case of a young patient treated for this rare disease since childhood to raise awareness among all medical staff, especially pediatricians, urologists and nephrologists, of this pathology which can be mitigated and whose progression can be slowed down if diagnosed at an early stage not like our patient necessitating liver-renal transplantation as the ultimate treatment.

Introduction:-

Primary hyperoxaluria Type I is an autosomal recessive disorder that affects 1 in 100,000-150,000 births in Europe, with a prevalence of 1-3 cases per million population [1]. It is caused by a mutation in the AGXT gene that results in a deficiency of alanine-glyoxylate aminotransferase (AGXT), an enzyme normally produced exclusively by hepatocyte peroxisomes and whose coenzyme is pyridoxine.

Excessive endogenous oxalate formation leads to increased urinary excretion of oxalate, which is responsible for the precipitation of calcium oxalate in the kidney, resulting in nephrocalcinosis and multiply recurrent lithiasis which may lead to end-stage renal failure, the management of which is not at all easy.

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CasePresentation:

We report here the case of a 20-year-old girl, 3rd of 3 siblings, from a consanguineous marriage, which presented at the age of 4 years to a pediatric service for a recurrent urinary infection. A renal ultrasound was performed to show nephrocalcinosis with multiple hyperechogenic lithiasis images (Figure 1), and an Abdominal X-ray showed several opacities projecting on the renal areas bilaterally (Figure 2). The patient was put on antibiotic prophylaxis with cefalexin. She was referred to a nephrology department for further investigation.

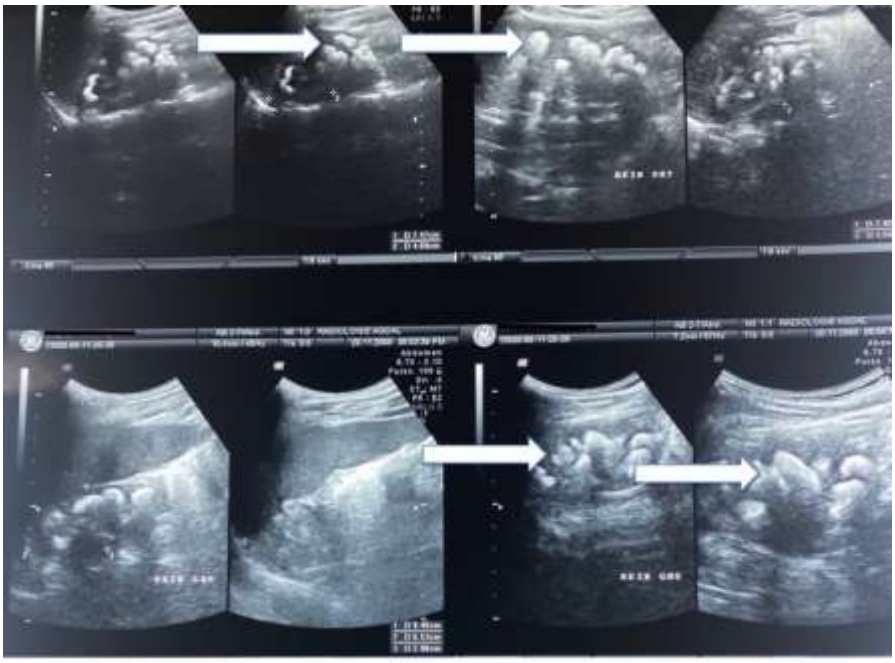

Figure 1:- Renal ultrasound showing several hyper-echogenic lithiasis images.

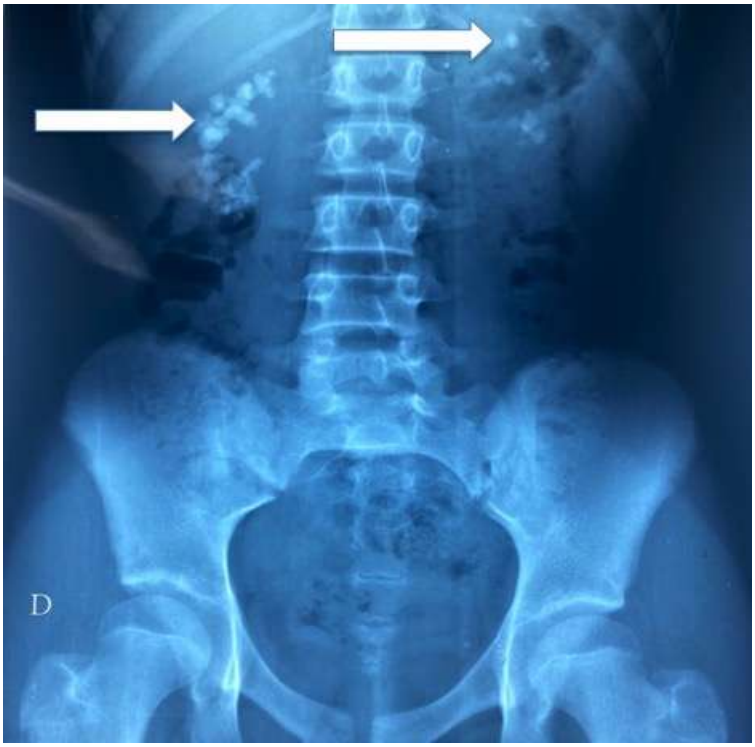

Figure 2:- Abdominal X-ray showing opacities over the bilateral renal areas.

In view of the suspicion of hyperoxaluria, a biological assessment was requested: crystalluria was performed, which showed insufcient dilution of the urine, major hyperoxaluria at 0.960 mmol / 24h, hypocitraturia at 0.14 and a ratio of oxalates to creatinine of 0.91 mmol/mmol, which is in favor of primary hyperoxaluria. One month later the patient spontaneously passed a stone, which on infrared spectrophotometric analysis was of an oxalic-calcium nature with an oxalic-dependent structure suggesting a particularly active lithogenic process dependent on major hyperoxaluria (whewellite).

A complete workup was requested from the patient, the result of which was as follows:
- Urea: 0.55 - Creatinine: 9.2 with a creatinine clearance of 53.8 ml/min/1.73 - Alkaline reserve: 17mmol/l - Parathormone: normal - Thyroid test: normal and Hypovitaminosis D at 11 micrograms/l

As recommended, the patient was put on an oxaloidal calcium inhibitor and pyridoxine in addition to cefalexin and vitamin D supplementation. Very good hydration was necessary.

Since then, every three months the patient was followed up in consultation by an ultrasound, crystalluria, E.C.B.U, and renal function with almost the same treatment being prescribed until 2016 (patient aged 13). And given the progressive alteration of the renal function, the removal of the stones is necessary according to the opinion of an urologist, and a CT scan revealed multiple diffuse and bilateral calcifc lithiasis with subcentimetric cortex.

Admitted to the operating room, an attempt to remove right kidney stones by lumbotomy was unsuccessful due to the risk of bleeding (hemostasis nephrectomy), and a double J probe was put in place with an exit on the toes. The double J probe was removed 03 months later. (Figure 3)

Figure 3:- Pediatric double J probe used in our patient.

Four years later, the renal function continued to worsen despite medical treatment, with a GFR of 25-ml/min/1.73 m. A second urologist's opinion was sought and another uroscanner was carried out (Figure 4), which still found kidney stones occupying all the excretory cavities of variable size and calcium density.

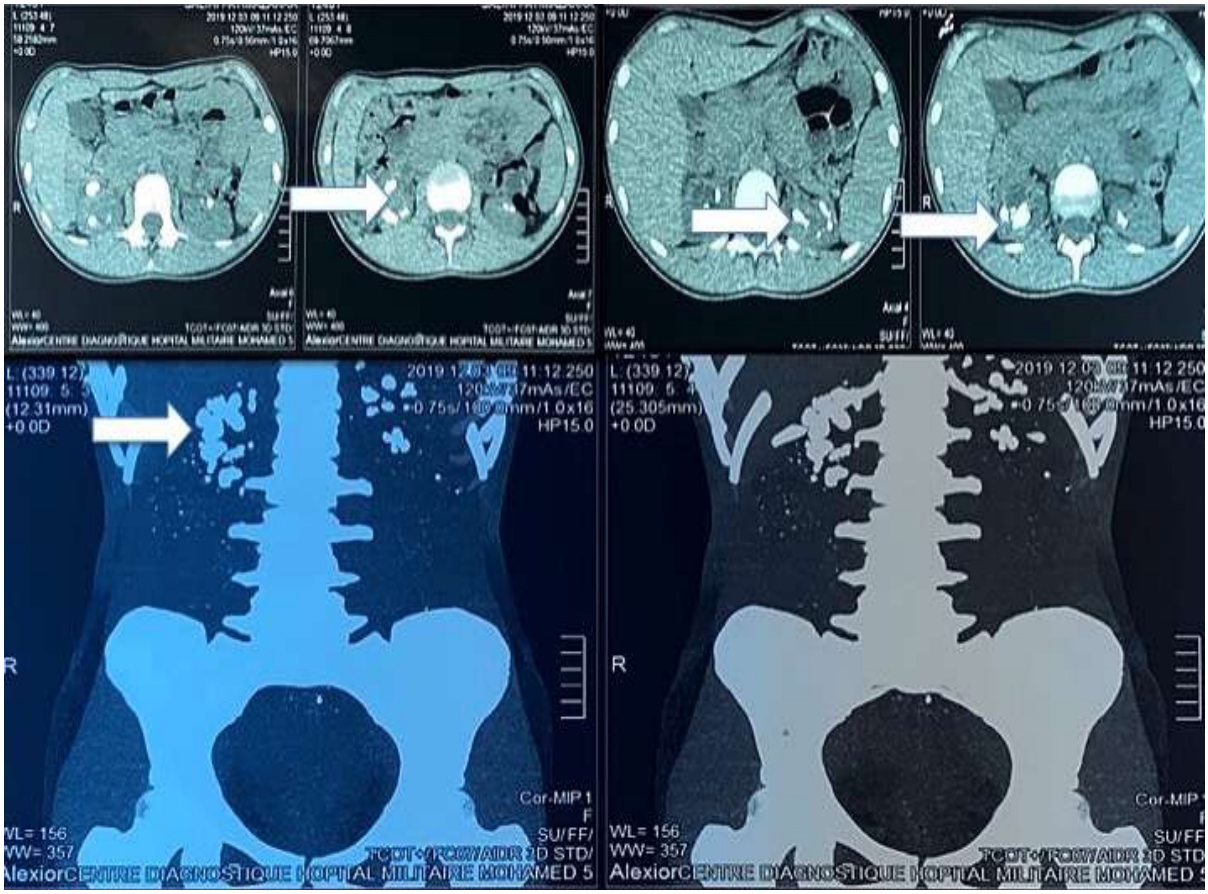

Figure 4:- CT-SCAN showing kidney stones occupying all excretory cavities.

A right percutaneous nephrolithotomy (PCNL) was performed with the extraction of 2 small stones without fragmentation and failure to extract the other stones.

Bilateral double J probes were placed (Figure 5) and the patient was scheduled for fexible ureteroscopy which itself was unable to extract the stones which were parenchymal since then the patient has been followed up in urology with iterative changes of the double J probe until the GFR reached 11 ml/min/1.73 m with the decision to remove the double J probe which was no longer useful.

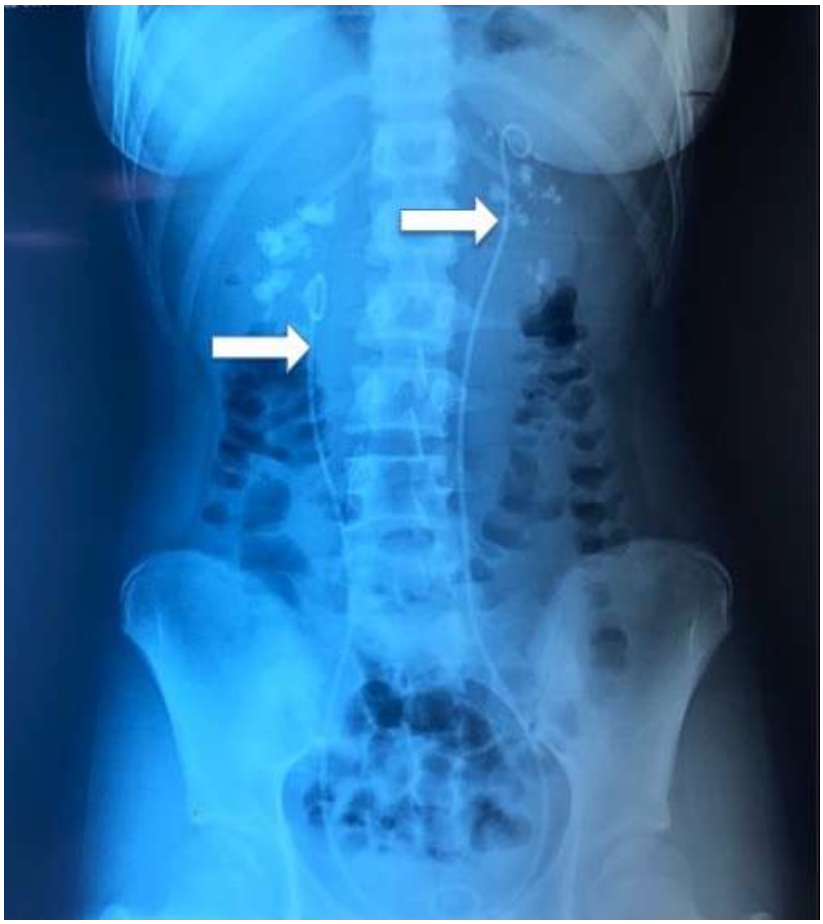

Figure 5:- Abdominal X-ray showing double J probe placement after all surgical alternatives have failed.

A multidisciplinary staff proposed the patient for possible combined liver-kidney transplantation.

Discussion:-

Primary hyperoxaluria is a rare condition with an estimated incidence of less than 1 case / million population / year [1]. It is a congenital anomaly of hepatic metabolism leading to an overproduction of oxalate with excessive urinary elimination. Three forms have been described in the literature, each corresponding to a particular enzyme deficiency, but all three are autosomal recessive. Primary hyperoxaluria type 1 is the most frequent form [2]due to a hepatic enzyme deficiency in AGX. Due to the rarity of the condition and the lack of awareness of hereditary kidney diseases that cause stones, it takes an average of 3 to 5 years from the first symptoms to diagnosis [1]. The combination of stones, nephrocalcinosis and impaired renal function is highly suggestive of HP1, especially when there is consanguinity, as in our patient.

The clinical presentation of our patient was similar to the literature: urinary tract infections secondary to recurrent urinary lithiasis from a young age with nephrocalcinosis [3-4].

The study of crystalluria, morphological analysis of the stone and examination by infrared spectrophotometry are essential in the diagnostic approach because they allow the identification of calcium oxalate monohydrate crystals (whewellite), which was the case for our patient.

In accordance with the literature, the diagnosis in our case was made by the combination of hyperoxaluria (urinary oxalate > 0.5 mmol/1.73 m2 per 24 h) or a urinary oxalate/creatinine ratio > 100 mmol/mol) and hyperglycolaturia (urinary glycolate > 0.5 mmol/1.73 m2 per 24 h), which is highly suggestive of HP1, even though hyperglycolaturia is not constant. Oxalemia (N < 6 μmol/L) is not sufficiently specific as the concentration usually remains normal as long as the renal function is preserved [5, 6]. However, when renal function is severely impaired (glomerular

filtration rate [GFR] < 20 ml/min/1.73 m2), oxalemia may be relevant to guide the diagnosis in patients never diagnosed with HP1.

Ultrasound examination of the urinary tract abdomen, also carried out in our patient, can reveal highly radiopaque kidney stones - usually rounded and lumpy, sometimes spiculated in the shape of a sea urchin, which explains the frequency of nephritic colic when these spiky forms migrate, and also nephrocalcinosis.

CT scan: allows the detection of calcifications that are not yet visible radiologically and their precise location, but its cost and irradiation do not allow it to be used as a screening examination.

These stones are often numerous, bilateral and often located in the pyelon and renal calyces, but are never coralliform. The association of nephrocalcinosis with oxalocalcic urolithiasis is strongly suggestive of HP I in young children [7,8].

Liver biopsy for the determination of AGXT activity is an invasive procedure not without potential complications. Its indication is nowadays very limited and in practice not recommended when the biochemical diagnosis of hyperoxaluria and hyperglycolaturia are concordant [9], which explains the fact that it was not performed in our patient.

Molecular diagnosis is the technique of choice for confirming the diagnosis of HP1, typing the genetic form and identifying families at risk [10]. This non-invasive technique is also used for prenatal diagnosis.

Conservative treatment should be initiated as soon as the diagnosis is suspected and even before it is confirmed. The aim is to reduce oxalate production and continuously increase the solubility of calcium oxalate in the urine [11]. The mainstay of treatment is hydration (2-3 L/m2 per 24 hours) both day and night.

Pyridoxine phosphate (vitamin B6) is the main coenzyme of AGXT. It significantly reduces oxaluria in one third of patients and therefore deserves to be tested systematically (5 mg/kg per day, increasing in steps if necessary, without exceeding 20 mg/kg) [12].

Potassium citrate - if glomerular filtration allows - (100-150 mg/kg per day), neutral phosphate or magnesium are essential to reduce calcium absorption and thus calciuria, but also to inhibit the crystallisation of calcium oxalate in the urine [1].

Our patient benefited from a quarterly prescription of these two molecules associated with adapted hydration and regular biological monitoring.

The use of diuretics should be cautious. Furosemide increases urine output, but has a calciuretic effect. On the other hand, the diuretic effect of thiazides (hydrochlorothiazide, 1 to 2 mg/kg/day) is less clear but they significantly reduce calciuria.

Reducing dietary oxalate intake has little effect on the course of HP1, as dietary oxalate accounts for no more than 5-10% of total renal oxalate elimination. However, vitamin C supplementation should be avoided as ascorbic acid is a precursor of oxalate [13].

Urological treatment of stone should avoid parenchymal aggression, which may alter the FG [14]. The use of minimally/micro-invasive endoscopic techniques, with or without laser, is always preferable. However, when faced with a large stone load, percutaneous nephrolithotomy (PCNL) has an excellent stone removal rate, except that this technique is more invasive and associated with more complications and a longer hospital stay.

Extracorporeal lithotripsy remains an acceptable option, but if nephrocalcinosis is present, parenchymal damage in the shock wave bundle may impair renal function [15].

All stone treatments in HP1 patients have the potential to alter the disease profileof the renal function and it is sometimes preferable to limit the use of double J probes.

This was the case with our patient after all surgical techniques for stone removal had failed in the face of nephrocalcinosis, and her treatment was finally limited to bilateral double J catheters. Urological indications are ultimately all delicate and should be entrusted to urologists experienced in the treatment of this condition [14].

At the end-stage chronic kidney disease, nephrectomy of clean kidneys may be proposed with a view to transplantation, in order to limit the risk of infection and episodes of obstruction.

Overall, dialysis is not suitable for the treatment of HP1 At the end-stage chronic kidney disease. Indeed, despite the low molecular weight of oxalate, dialysis does not allow the excessive overproduction of oxalate in the liver to be balanced: this production is 4 to 7 mmol/1.73m2/24 h whereas purification by conventional dialysis is only 1 to 2 mmol/1.73m2/24 h), so that tissue overload is inexorable. Such an option is therefore unacceptable, both in terms of quality of life and morbidity or mortality.

This is because haemodialysis only removes circulating soluble oxalate and leads to a rebound in concentration from the slow-replenishing compartment (skeleton), so the benefit of repeated sessions is much greater than that of prolonged sessions; daily haemodialysis is therefore recommended.

Peritoneal dialysis does not provide sufficient oxalate removal but, particularly in cases of infantile oxalosis, the combination of daily haemodialysis and peritoneal dialysis provides relatively efficient removal, limits systemic exposure and avoids post-dialytic oxalate rebound, but at the cost of poor quality of life [16].

Transplantation: remains the ultimate treatment for HP1 and several transplantation strategies are possible for primary hyperoxaluria type 1:

Isolated renal transplantation allows the removal of soluble calcium oxalate from the body. Persistent hepatic hyperproduction of oxalates leads to graft destruction [17]. Isolated renal transplantation is therefore a priori contraindicated because of the risk of renal recurrence and the lack of efficacy on systemic damage [1].

Isolated liver transplantation can correct the enzyme deficiency. This strategy is only of interest when renal function is preserved [18].

Combined liver-renal transplantation is the best strategy in cases of end-stage renal failure or at the hemodialysis stage. Sequential transplantation starting with liver transplantation and then, after purification of the body of calcium oxalates, with renal transplantation is the best strategy. Our patient is proposed for the 3rd option given the end-stage renal failure [19].

At present, therapeutic hope is represented by the satisfactory results of recent studies showing the efficacy of lumasiran: an RNAi therapeutic against type 1 primary hyperoxaluria [20].

Conclusion:-

Primary hyperoxaluria type 1 is a serious condition whose diagnosis is often delayed, even though it is fairly easy to confirm when it has been suggested. Treatment is burdensome for patients, their families and society. Genetic counselling in families at risk should be part of the management to improve the prognosis of this disease. However, there are many research perspectives, for which the development of an international database is underway.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Author contributions

All authors contributed at all stages

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Non.

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