The Primary Hyperoxalurias

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Primary hyperoxaluria (PH) results from endogenous (primary) overproduction of oxalic acid, as opposed to secondary hyperoxaluria, which is attributable to increased intestinal absorption (enteric) or excessive intake (dietary) of oxalate. Why are nephrologists interested in PH type 1 (PH1), the prevailing type, although it is far from being a primary renal disorder? First, the clinical treatment of patients with this “nephrologic liver disease” is quite challenging, particularly in end-stage renal failure (ESRF). Second, the study of PH1 has yielded better understanding of the pathogenesis of calcium oxalate (CaOx) crystal deposition and stone formation in general, with this disease serving as a model of nephrocalcinosis and urolithiasis. Finally, fascinating insights into the mechanisms of cellular trafficking have been obtained from the study of PH1; however, many questions remain unresolved. It has also become apparent that PH encompasses more than PH1 and PH2, and some patients who were previously classified as having secondary hyperoxaluria might actually have a type of PH.

PH1

Metabolic and Genetic Basis

PH1, which is an autosomal recessive disease, is caused by a defect in glyoxylate metabolism attributable to low or absent activity of the liver-specific peroxisomal enzyme alanine/glyoxylate aminotransferase (AGT) (392 amino acids, 43 kDa) (Figure 1) (1,2). As a result, urinary excretion of oxalate and (in most cases) glycolate is greatly increased (2). Although massive intrarenal CaOx deposits were noted by Lepoutre in 1925 for a pediatric patient who was surgically treated for urolithiasis (abstract cited in reference 2), the disease was not named PH until 1957 (3) and the metabolic defect was localized in liver peroxisomes (therefore not within the cytosol, as previously thought) in 1986 (1). In contrast to PH1, patients with a primary peroxisomal disorder such as the Zellweger syndrome do not exhibit hyperoxaluria (2). Except for the AGT defect, peroxisomes in PH1 are normal in almost every respect; they appear only slightly smaller in electron microscopic evaluations (4). The functional deficiency of AGT in PH1 results in a failure to detoxify glyoxylate within the peroxisomes. Instead of being transaminated to glycine, glyoxylate is oxidized to oxalate and/or reduced to glycolate, resulting in greatly increased urinary excretion of oxalate and glycolate (Figure 1) (1,2,4). Glyoxylate itself is synthesized within the peroxisomes from glycine and glycolate (2).

The gene coding for AGT, i.e., AGXT, is located on chromosome 2q37.3 and consists of 11 exons spanning approximately 10 kb (2,5). More than 30 mutations have been identified to date. There is considerable molecular heterogeneity; many patients are compound heterozygotes (frequently with only one allele identified), whereas populations with high rates of consanguinity, e.g., Israeli Arabs (6) or Northwest Africans (7), exhibit mutations in a homozygous pattern. One-half of the patients exhibit no detectable AGT catalytic activity, whereas the other half exhibit residual (2 to 48%) AGT activity (2,4).

Why do individuals with residual AGT activity become ill, not differing clinically from patients with absent AGT activity? AGT is mistargeted from the peroxisomes to the mitochondria, as elegantly demonstrated by Danpure and co-workers (2,4,5). Although such patients often exhibit considerable residual enzymatic activity, only 10% of the immunoreactive AGT (cross-reacting material–positive) is localized within the peroxisomes; 90% is found within the mitochondria, where it is metabolically inactive. In his laureate speech, Günter Blobel, the 1999 recipient of the Nobel Prize in Medicine, referred specifically to PH1, in which the altered sorting signal leads to erroneous intracellular localization of the enzyme (http://www.nobel.se). This protein-trafficking defect is unparalleled in human subjects (2). It is observed in approximately 30% of all patients with PH1, usually as the result of a 630G→A mutation (associated with a Pro11Leu polymorphism), which leads to a Gly170Arg amino acid substitution, or, less often, as the result of a 576T→A mutation (2,8).

Pathophysiology

Urine is a saturated solution, and its concentration can change very drastically within a short time (9). Stone formation or the development of nephrocalcinosis thus occurs when the delicate interplay between promotors (in PH1, especially oxalate) and inhibitors (e.g., citrate, magnesium, and glycosaminoglycans) of crystal formation is disturbed (9,10). In PH1, the urine is supersaturated with respect to CaOx (urinary CaOx
saturation of >10 relative units) (2,8,11). This produces renal calculi, medullary nephrocalcinosis, or both.

Oxalate is freely filtered in the glomerulus and is both secreted and reabsorbed in the proximal tubule (2). Oxalate transport across proximal tubular cells is complex, because this anion plays a role as a recycling substrate that functionally links the transcellular absorption of chloride to that of other anions (bicarbonate and sulfate) (12). At the basolateral membrane, oxalate enters the cell in exchange for sulfate or bicarbonate, via Sat-1 (12). At the luminal brush border membrane, oxalate is transported out of the cell in exchange for chloride and is transported back into the cell in exchange for sulfate. The overall result is a net secretion rate of 10 to 30%, corresponding to fractional oxalate excretion ($C_{\text{ox}}/C_{\text{in}}$) of 1.09 to 1.28 (2).

With physiologic concentrations of oxalate, occasional crystals either are passed as crystalluria particles or are endocytosed by renal epithelial cells (13). Endocytosed crystals are eliminated or are exocytosed to the basolateral side of the cells. From there, the crystals migrate to the interstitium, where they may eventually be destroyed by local inflammatory reactions involving macrophages (14). In PH1, far more oxalate is filtered in the glomeruli than under normal conditions, leading to extremely high oxalate concentrations within the proximal tubular cells. Until recently, these high oxalate concentrations were not considered to be harmful themselves, apart from the risk of CaOx deposit formation in the renal interstitium, followed by foreign-body reactions. However, it is now well established that high oxalate levels have direct toxic effects on renal tubular cells (15). Oxalate reduces both the growth rate and life span of LLC-PK1 cells (which resemble proximal tubular cells), in a concentration-dependent manner (15,16). Whereas oxalate acts as a mitogen at low concentrations, it is a toxic agent at high concentrations (16). These negative effects at the cellular level resemble those observed in other tissues after oxidative stress (15). Indeed, oxalate seems to promote the production of free radicals, which may explain its cellular toxicity (15,17). Because such effects are clearly concentration-dependent, this mechanism may directly contribute to rapid deterioration of renal function in PH1, which is much greater than that observed with nephrocalcinosis of other origins. In addition, the high plasma oxalate levels of patients with PH1 and renal insufficiency may exert toxic effects on other organs and tissues (18).

Both plasma oxalate levels and plasma CaOx saturation values are significantly higher for patients with PH1 than for normal control subjects, even with normal renal function (19–21). The two parameters increase concomitantly (19–21) and are inversely correlated with the GFR (19). Plasma CaOx supersaturation (plasma CaOx saturation of >1), with plasma oxalate levels of >30 μM, is observed with a GFR of <45 ml/min per 1.73 m², in contrast to non-PH1 patients, for whom supersaturation occurs only with a GFR of <8 ml/min per 1.73 m² (18,19,21). CaOx crystal deposition therefore begins early in PH1, and patients are at risk of systemic CaOx deposition before the stage of chronic renal failure (19).

**Diagnosis**

Unfortunately, the diagnosis of PH1 is often overlooked or delayed; therefore, different diagnostic procedures are briefly discussed here.

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**Figure 1.** Metabolic defects in primary hyperoxaluria type 1 (PH1) [alanine/glyoxylate aminotransferase (AGT)] and PH2 [glyoxylate reductase (GR)/hydroxypyruvate reductase (HPR)]. Glyoxylate reductase also exhibits hydroxypyruvate reductase activity. GO, glycolate oxidase; DAO, d-amino oxidase; LDH, lactate dehydrogenase.
Analysis of Urine. Hyperoxaluria is the hallmark of PH1. Urinary oxalate excretion is usually greatly elevated among patients with PH1 and recurrent urolithiasis and/or nephrocalcinosis, exceeding 2 mmol/24 h per 1.73 m$^2$ and sometimes even 4 mmol/24 h per 1.73 m$^2$ (normal, <0.5 mmol/24 h per 1.73 m$^2$ or <45 mg/24 h per 1.73 m$^2$) (2,8). However, family studies have demonstrated that some untreated patients with PH1 may exhibit only slightly elevated (0.5 to 1 mmol/24 h per 1.73 m$^2$) or even normal urinary oxalate excretion (22). Frequent sources of error are (1) incorrect urine collection (acidification to pH <2 is required to prevent deposition of insoluble CaOx), (2) failure to convert 24-h oxalate excretion values for pediatric patients to the adult surface area (1.73 m$^2$) or to consult age-related tables for oxalate/creatinine ratios (8,10), and (3) renal insufficiency associated with oxalate retention and reduced urinary excretion. In such cases, plasma oxalate determinations may be helpful. Glycolate levels are elevated in only approximately two-thirds of patients with PH1; therefore, findings of normal values (which are in the same range as those for oxalate, in milligrams or millimoles) do not exclude this diagnosis (2,8).

Plasma Oxalate Measurement. In patients with PH1, plasma oxalate levels, which are already elevated (>6.3 μM) with normal renal function, are significantly higher (>80 to 100 μM) in ESRF, compared with those for patients without PH1 (40 to 60 μM) (18,19,21).

Liver Biopsy Assessment. A definitive diagnosis (which is essential if liver transplantation is being considered) requires assessments of AGT activity and immunoreactivity in hepatic tissue (minimum of 2 mg), unless the diagnosis has been established at the molecular level (2,8). Testing for both PH1 and PH2 can be performed with the same needle-biopsy specimen of the liver (23).

DNA Analysis. Patients with PH1 are frequently compound heterozygotes, and the mutation on the second allele often remains unidentified, which renders DNA analysis impractical as a diagnostic procedure (2,8). However, selective screening among populations with high incidences of specific homozygous mutations (e.g., Ile244Thr in North African patients) would be feasible (7). Prenatal diagnosis can be performed by linkage analysis using chorionic villous biopsy samples, if the family has been demonstrated to be informative (24). Genetic counseling must take into account, however, that the fact that family members carrying identical mutations may exhibit grossly discordant clinical features (22).

Stone Analysis. The calculi of patients with PH1 consist almost exclusively of pure CaOx monohydrate (whewellite); this finding may yield a diagnostic clue (25,26). Microscopic analysis reveals a characteristic subtype (subtype 1c) that is virtually pathognomonic for PH1 (25).

Bone biopsies for patients with renal failure, to demonstrate birefringent CaOx crystals, were previously used for diagnosis. Eyeground examinations are diagnostically important (Figure 2).

Clinical Manifestations

Recurrent urolithiasis and nephrocalcinosis are the main symptoms, and the combination of the two conditions, leading to progressive loss of renal function, is characteristic for PH1 (Figure 2). One-half of the patients exhibit their first symptoms by the age of 5 yr (range, 1st month of life to 6th decade) (27,28). Diagnosis is usually delayed by ≥5 yr, except among infants (28). Although PH1 is a monogenic disease, the clinical severity is not correlated with the mutation or the degree of residual functional AGT activity (2,4,22). The clinical, biochemical, and genetic heterogeneity is very large, with some patients presenting in infancy with renal failure and others experiencing only occasional passage of stones in adult life, with maintained renal function (2,4,22,27,28). Family screening has demonstrated that some patients are completely without symptoms (with neither nephrocalcinosis nor stones) (22,28). Even members of the same family, with identical mutations, may exhibit completely different clinical phenotypes, e.g., severe infantile oxalosis, compared with absent clinical findings (22).

In a malignant variant (infantile PH1), the first symptoms occur very early (median age, 4 mo), and affected infants present at a median age of 6 mo with the triad of a failure to thrive, severe metabolic acidosis, and anemia, all of which are secondary to renal failure (29). This infantile form is characterized by rapid progression to ESRF and severe systemic oxalosis (29). Why these infants rapidly develop diffuse nephrocalcinosis (Figure 2) but not urolithiasis is not clear.

Systemic Oxalosis. Oxalate is systemically deposited when the critical saturation point for plasma oxalate (plasma oxalate levels of >30 μM) is reached, i.e., early in renal insufficiency (19). Deposition occurs in every organ and tissue except the liver and leads to disastrous complications, which should be prevented by all possible means. The bones are the most crippling site of CaOx deposition. The bone oxalate content in ESRF is considerably higher (15 to 910 μmol oxalate/g bone tissue) than that among patients without PH1 (2 to 9 μmol/g) (30). The lesions are characteristic both in x-rays (radiodense metaphyseal bands, a “bone-within-bone” appearance, and diffuse demineralization with a coarse trabecular pattern) and in histologic assessments (intraosseous tophi of CaOx and granulomas replacing bone marrow) (31). Clinical manifestations of oxalate osteopathy are pain, spontaneous fractures, and erythropoietin-resistant anemia (31,32). Retinal CaOx deposits, which are easy to diagnose, may be one of the first obvious signs of systemic oxalosis (Figure 2) (33). Additional important sites of CaOx deposits are the media of the arteries (with subsequent ischemia and gangrene), the peripheral nervous system (neuropathy), the myocardium (atrioventricular block), the thyroid gland, and the skin (livedo reticularis).

Epidemiologic Features and Prognoses

Because the diagnosis is often delayed or overlooked (27,28,34), the incidence of PH1 is easily underestimated. Data from the United Kingdom, Switzerland, and France suggest that 1 in 60,000 to 120,000 children has PH1 (27,28,35). The
disease is far more common in certain countries such as Tunisia, where PH1 is the cause of ESRF for 13% of pediatric patients, compared with <0.7% (of those treated for ESRF) in North America and Europe (6,35). Clinical reports on PH1 are biased; of 330 patients reported, one-half were experiencing ESRF by the age of 15 yr (36). This finding contrasts with data from surveys performed in Switzerland and France, which demonstrated that ESRF occurred in 20% of patients by the age of 15 yr and in 50% of patients by the age of 25 yr (27,28). However, infantile oxalosis has a particularly poor prognosis, with one-half of the patients experiencing ESRF at the time of diagnosis and 80% developing ESRF by the age of 3 yr (29).

The prediction of outcomes for individual patients is very difficult, if not impossible. Indeed, almost no renal disease is more problematic in this respect. Patients with PH1 with GFR of >50 ml/min may remain in stable condition for many years but may rapidly and irreversibly lose residual function during episodes of dehydration, urinary obstruction, or noncompliance. Nevertheless, the prognoses for patients with PH1 tend to be considerably better, if the disease is properly treated, than suggested in the literature.

**Treatment**

**Conservative Therapy.** The aims of therapy are to decrease oxalate production and to increase the urinary solubility of CaOx. The importance of close follow-up monitoring and of preventive measures to avoid episodes of dehydration cannot be overemphasized.

**Pyridoxine.** Pyridoxal phosphate is an essential cofactor for aminotransferases such as AGT, and pharmacologic doses of pyridoxine (stepwise increases from 5 to 20 mg/kg per d, according to urinary oxalate excretion) are able to significantly reduce (by at least 30%) hyperoxaluria in one-third of patients (35). The patients most likely to respond are those with resid-
ual AGT activity (37). For assessment of pyridoxine responsiveness, reliable baseline values (a minimum of three) for urinary oxalate excretion are required. A trial of not less than 3 mo is warranted [determination of plasma oxalate levels is helpful in renal insufficiency (19,37)], although the effects are visible within 1 to 2 wk in most instances. Young infants may exhibit different behavior. Indeed, a 1-mo-old infant (with a 630G→A mutation) who failed to respond to high doses of pyridoxine in 2 mo exhibited a full response, within 1 wk, 14 yr later (E. Leumann, unpublished observations). Very high doses (>30 mg/kg) are unnecessary and may lead to peripheral neuropathy. Occasionally, even low doses (20 mg/d) of pyridoxine may suffice (38). Pyridoxine responsiveness is still poorly understood at the molecular level (2). Direct pharmacologic interventions to reduce the glyoxylate or glycolate metabolism is not recommended, although ascorbic acid (a precursor of oxalate) contributes little to hyperoxaluria.

Extracorporeal shock wave lithotripsy should be used with caution and only after generous hydration, because it may seriously harm the kidneys of patients with PH1 and nephrocalcinosis (43).

**Treatment in ESRF**

**Dialysis.** Neither hemodialysis nor peritoneal dialysis is able to keep pace with the endogenous production rate of oxalate, much less reduce the body oxalate burden (20,44). In fact, the weekly oxalate dialysance of renal replacement therapies (6 to 9 mmol/wk per 1.73 m² surface area) equals only the endogenous oxalate production of 2 to 3 d (44). Therefore, CaOx steadily accumulates, and CaOx crystals are deposited in other organs (systemic oxalosis), in addition to the kidney. Although the oxalate clearance is greater with hemodialysis (approximately 120 ml/min) than with peritoneal dialysis (approximately 7 ml/min), weekly oxalate elimination values are similar for the two renal replacement therapies (44). Not even the combination of the two therapies or the use of high-flux dialyzers, or hemofiltration, is able to prevent further oxalate retention (45); plasma oxalate levels and CaOx saturation values remain extremely elevated or increase even further (18). Therefore, intensified hemodialysis, with five or six 5-h sessions each week, may be necessary until transplantation is performed.

**Isolated Kidney Transplantation.** Except among the few patients who respond well to pyridoxine (37), recurrent nephrocalcinosis and stone formation are expected to occur. Particular risk factors are long ischemia times (cold or warm) and any periods of graft dysfunction. The results of isolated, mostly cadaveric, kidney transplants performed in Europe in the 1980s were very poor, with 3-yr survival rates of only 20% for grafts and 74% for patients (46). This treatment modality has thus been largely abandoned there, in favor of combined liver/kidney transplantation. In contrast, isolated kidney transplantation (preferably with living related donors) is still favored in the United States (47). The medium-term results were acceptable, with actuarial 6-yr survival rates of 84% for patients and 51% for grafts; however, the 10-yr graft survival rate was only 35% (47).

**Combined Liver/Kidney Transplantation.** The first liver transplant for a patient with PH1 was performed in 1984, before the basic enzymatic defect had been identified (48). Because the metabolic defect is in the liver, it is necessary to perform a total hepatectomy, although the liver is normal in every other respect (2). Auxiliary liver transplantation is not an option, because it would not affect oxalate overproduction by the patient’s own liver (2,49). To date, >100 combined liver/kidney transplants have been performed in Europe, according to the European OXALOSIS Registry (Cambridge, UK) (50,51). Actuarial 5-yr survival rates (for 98 grafts in 93 patients) were 80% for patients and 71% for liver grafts (35,50,51). Notably, renal function has remained stable, with creatinine clearance rates of 40 to 60 ml/min per 1.73 m² after 5 yr.

Specific risk factors are young age (<5 yr) and long duration of dialysis (>2 yr) (35,50,51). If the renal graft immediately
begins to function, there is no reason to perform additional hemodialysis or hemofiltration. Administration of generous amounts of fluids and treatment with alkali citrate during the first months are essential, because of the slow mobilization of the accumulated body stores of CaOx (18,37). In fact, both plasma oxalate levels and plasma CaOx saturation values, as well as urinary oxalate excretion, remain elevated for several months or even years after successful combined liver/kidney transplantation (2,18,37). In contrast, increased levels among patients without PH are normalized within 3 wk after transplantation (18,52).

Preemptive (Isolated) Liver Transplantation. The rationale for preemptively performing liver transplantation, instead of waiting until ESRF occurs, initially seems straightforward (49). Indeed, if liver transplantation were a relatively harmless procedure and there were no shortage of organs, preemptive transplantation would probably be an accepted treatment method for many patients with PH1. However, the risks of graft loss or even the death of a patient who might have lived several years longer without any intervention raise serious ethical questions. Of additional concern is the need for immunosuppressive therapy with drugs that may severely compromise residual renal function and accelerate the onset of renal insufficiency. To date, more than a dozen patients with PH1 who were not experiencing renal failure have been treated in this way, with reasonable results (49). However, some of the patients might have maintained their renal function without intervention. The major problem concerns the timing of transplantation, because the natural course of the disease is so difficult to predict. Obviously, isolated liver transplantation can be successful only if renal failure is not too far advanced; the minimal GFR is probably 40 ml/min, or even 50 to 70 ml/min, with plasma oxalate levels of <30 μM (8,18). If the GFR is <40 ml/min per 1.73 m², there is a high risk of rapid further decline, necessitating secondary kidney transplantation (49). Obviously, the overall results of isolated liver transplantation should be better with better residual renal function. However, with better preservation of renal function, the risks and efforts involved become increasingly disproportionate, with respect to the potential benefits of such a procedure.

Treatment in ESRF among Infants and in Developing Countries. Therapy for infants with the malignant variant of PH1 presents particular problems. Because of their small size, such patients require peritoneal dialysis for extended periods, which is invariably leading to progressive systemic oxalosis, until combined liver/kidney transplantation becomes technically feasible. Some developing countries exhibit a high incidence of PH1 but lack the necessary infrastructure and resources for organ transplantation (29). Because dialysis is not a suitable alternative treatment for PH1, except for very limited periods, therapeutic withdrawal in both situations is an option that raises serious ethical questions (29).

Prospects for Gene Therapy. Enzyme replacement therapy via liver transplantation might be considered an extreme form of gene therapy. Considerable problems must be solved before gene therapy in the strictly defined sense becomes applicable. By analogy to auxiliary liver transplantation (which does not work because oxalate is still produced in excess), gene therapy would require transfection of far more than 20 or 30% of liver cells, which is impossible to perform with current vector technology (53). Another potentially beneficial approach involves increasing the level of ATG expression (i.e., AGT activity) per cell by using superactive AGT constructs (C. J. Danpure, personal communication, July 2000); this approach would not yield higher overall transfection efficiency (i.e., the percentage of cells expressing AGT). Whether gene therapy alone, even with such constructs, would be able to compensate for the ongoing abnormal endogenous oxalate production by nontransfected cells is a matter of debate. The question of how often such gene therapy would need to be repeated is also unresolved.

PH2

PH2 is a rare disorder, with <30 reported cases (54,55), and is likely to be underdiagnosed (35). Clinical manifestations are not as severe as in PH1 and consist primarily of urolithiasis. Nephrocalcinosis is rather unusual (occurring in 12% of patients), and systemic involvement is rare (54). The median age at onset is 15 yr; ESRF does occur but has not been observed in the pediatric age group. The hallmarks of PH2 are high levels of urinary excretion of oxalate and L-glyceric acid [normal, <28 mmol/mol creatinine (54)]; however, normal L-glyceric acid excretion was observed in one case (G. Rumsby, personal communication, November 2000).

PH2 results from the deficiency of a cytosolic enzyme with glyoxylate reductase, hydroxypyruvate reductase, and D-glycerate dehydrogenase activities (Figure 1) (23,55,56). The tissue concentration of glyoxylate reductase/hydroxypyruvate reductase is high in the liver but low in the kidneys, lymphocytes, and fibroblasts (23). Diagnoses of PH2 can be confirmed by measurements of the glyoxylate reductase activity in liver biopsy samples (23). The responsible gene, GRHPR, was recently mapped to the centromeric region of chromosome 9 and contains nine exons, spanning 9 kb (55,56). Several mutations (mostly homogeneous) have been reported (57).

As for PH1, supportive treatment includes confirmation of high fluid intake, administration of crystallization inhibitors, and prevention of complications; there is no rationale for the use of pyridoxine. Kidney transplantation does lead to recurrence, because hyperoxaluria and elevated L-glycerate excretion persist (54). More biochemical data are required before liver transplantation can be recommended (54).

Atypical PH

As has been the case for other metabolic diseases, the advent of enzyme measurements has clearly demonstrated that PH comprises more than PH1 and PH2. There have been reports of several pediatric patients, for whom both PH1 and PH2 were definitely excluded and who did not present evidence of secondary hyperoxaluria, who exhibited early (average age, 2 yr) manifestations of urolithiasis attributable to hyperoxaluria, sometimes combined with hypercalcuria (26,35,58). Should this condition be termed PH3? There is considerable evidence
that this condition is heterogeneous and involves further subtypes (e.g., PH3 and PH4).

Conclusions

Much progress has been made in recent years and the molecular genetic bases and enzyme diagnostic techniques have been firmly established for PH1 and PH2. However, considerable effort is required to explain the discrepancy between genotypes and phenotypes in PH1 and to define the underlying metabolic defects in atypical PH. Early diagnosis and aggressive conservative treatment are essential. Some controversy exists regarding the optimal therapy for patients with PH1 and renal insufficiency. The fact that no form of dialysis therapy is available is an important consideration. Intensified research in PH could also benefit the large numbers of patients with secondary hyperoxalurias, a goal also addressed by the Oxalosis and Hyperoxaluria Foundation (www.ohf.org).

References

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