ACUTE KIDNEY INJURY IN CHILDREN AND ADOLESCENT POISONING – PREVALENCE, ETIOLOGY AND RISK FACTORS

Alexandru-Ioan Ulmeanu[1], Aurel Bizo[2], Coriolan Ulmeanu[1]
[1]"Grigore Alexandrescu" Emergency Children's Hospital, Bucharest
[2]Emergency Children's Hospital, Cluj-Napoca

ABSTRACT

Objectives. The incidence and prevalence of renal disease in actual children poisoning is not fully known because renal structural and functional changes caused by nephrotoxins are nonspecific and toxic etiology is often overshadowed. This study aims to assess the prevalence of toxic nephropathies in a pediatric population, the etiology, clinical and laboratory aspects, prognostic factors, frequency of use of extra renale puration techniques and their impact on survival.

Materials and methods. We conducted an observational, retrospective, multicentric study, over a period of 10 years, between 2003 and 2012, on 82 patients aged 0-18 years from two pediatric poison centers: the department of Toxicology SCUC "Grigore Alexandrescu" Bucharest and the Department of Pediatric Nephrology and Toxicology at the Emergency Clinical Hospital for Children in Cluj-Napoca. In the study group were included patients with acute intoxication who presented acute kidney injury defined by the AKIN criteria.

Results. The etiology of poisoning that have associated acute kidney injury is dominated by drugs – 36.6%, followed by mushrooms – 24,4%, insecticides – 18.3% and alcohols – 11%. In smaller percentages we noted poisonings with caustic substances, hydrocarbons, nitrites and lead. Looking in detail we can observe that for the etiology of drug poisonings multidrug intoxications prevailed followed by poisonings with antibiotics most commonly gentamicin. In the case of multi drug poison ings the substances most frequently involved were: combination of Paracetamol, NSAIDs andMetamizol.In mushroom poisonings, in most cases were involved mushrooms with long incubation period probably Amanita Phalloides. For the Insecticide poisonings the etiology was represented mainly by organophosphorus and carbamate insecticides. The etiology of alcohol poisoning most commonly included cases of ethylenglycol. On the group of 82 cases studied, 26 deaths were recorded, mortality was 32%. We observed that oliguria, anuria, edema, hemorrhagic manifestations, polypnea, signs of shock, coma, and hepatic hepatocytolisis were risk factors for death in our study. The methods of extrarenal epuration or renal replacement treatment were carried out in 41% of cases. They were not protective factors in the study group.

Conclusions. Acute poisoning cases in children show asignificant increasein recent years in our country. The cases oftoxic acute renal injury often have severe prognosis. Associated risk factorsshould be identified and diagnosed quickly to establish aprioritized early and effective treatment.

Keywords: toxic nephropathy, acute kidney injury, nephrotoxicity

INTRODUCTION

Acute poisoning in children is a major public health issue because poisoning represent about 10% of the accidents of every day life. The incidence and prevalence of renal disease in actual children poisoning is not fully known because renal structural and functional changes caused by nephrotoxins are nonspecific and toxic etiology is often overshadowed. As in adults, the combination of acute kidney injury (AKI) in pediatric pathology increase mortality, length of hospitalization and worsens the long term prognosis. Renal impairment in severe acute poisoning in children most frequently causes acute kidney injury. Prospective studies in the literature report an incidence of acute kidney injury in intensive care units from 2.5% to 4.5% (1). In hospitalized patients the main causes are: hemolytic uremic syndrome, ischemia, sepsis and pharmacological agents (2). In this study, we

Coresponding author:
Alexandru-Ioan Ulmeanu, "Grigore Alexandrescu" Emergency Children's Hospital, 30-32 Iancu de Hunedoara Blvd., Bucharest

aimed to evaluate the prevalence, causes and prognostic factors of acute poisonings complicated with AKI.

MATERIALS AND METHODS

We conducted an observational, retrospective, multicentric study, over a period of 10 years, between 2003 and 2012, on 82 patients aged 0-18 years that had been diagnosed and treated during the period in two pediatric poison centers: in the department of Toxicology SCUC „Grigore Alexandrescu" Bucharest and in the Department of Pediatric Nephrology and Toxicology at the Emergency Clinical Hospital for Children in Cluj-Napoca. In the study group were included patients with acute intoxication who presented acute kidney injury defined by the AKIN criteria (3). We used these criteria because in the study we could not assess properly retrospectively the creatinine clearance (4). We followed: distribution by age, sex and origin, etiology, intent, clinical and laboratory aspects, prognostic factors, length of stay and survival, frequency of use of extrarenal epuration techniques and their impact on survival.

RESULTS AND DISCUSSION

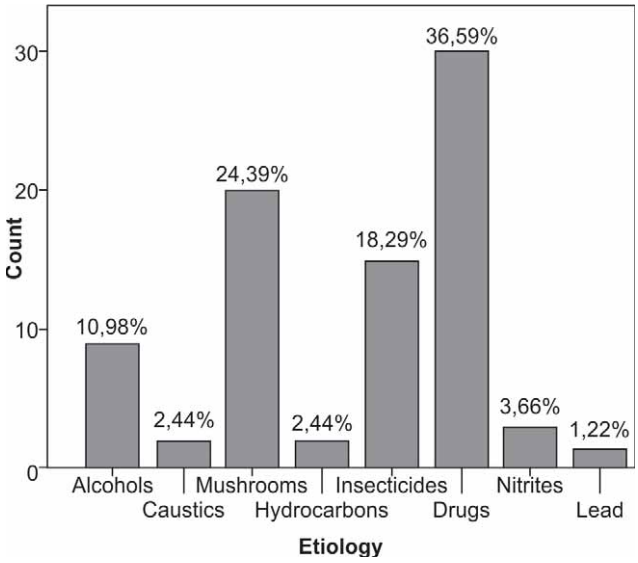
a. Epidemiology of toxic nephropathies

In the time period studied there were hospitalized and treated in the toxicology department of SCUC „Grigore Alexandrescu a number of 6556 poisonings, with an average of 650 poisonings per year, and in the Department of Nephrology - Toxicology of Cluj in the last 10 years a number of 1800 poisonings were reported. In both poison centers we observed an 15% increase in the number of cases. We noted that toxic renal injury was present in 82 cases, its prevalence was approximately 1%. AKIN criteria include three stages of acute kidney injury corresponding to the three letters RIFLE acronym namely RISK = 1 INJURY = 2 FAILURE = 3 In the analyzed group we observed a much higher frequency of stages 3 and 2 of AKI in a cumulative percentage of 85% Stage 3 was found in 51% of cases and stage 2 in 34% of cases. Stage 1 was present only in 15% of cases.

Mean age of patients in the study group was 8.5 years. Analyzing the distribution of patients by age and gender we observed two peaks of incidence: between 1-4 years 25.6% in which both sexes are equally represented, this is the age group were unintentional acute poisonings are more frequent and the second peak of incidence, 24.4% between 15-18 years with a greater predominance of females, which are mostly cases of suicide attempts. The lowest age recorded was 1 month in an infant with severe nitrite posioning. In the study group the majority of cases were unintentional poisonings from the 82 cases 81.7% were home accidents. This can be explained by the large number of mushroom and insecticide poisonings observed in the study group.

b. Etiology of toxic nephropathies

The etiology of poisoning that have associated acute kidney injury is dominated by drugs – 36.6%, followed by mushrooms – 24,4%, insecticides – 18.3% and alcohols-11%. In smaller percentages we noted poisonings with caustic substances, hydrocarbons, nitrites and lead.



GRAPHIC 1. *Etiology of toxic nephropathies*

Looking in detail we can observe that for the etiology of drug poisonings multidrug intoxications prevailed with 13 cases followed by poisonings with antibiotics most commonly gentamicin with 6 cases, and vitamin D intoxication and anesthetic substances 3 cases, and carbamazepine, paracetamol, opioids, digoxin, chemotherapeutic substances one case only.

During treatmentwith aminoglycosidesacute kidneyinjury with acute tubular necrosis(ATN) may occurat any dose.The incidence ofrenal dysfunctionvaries between5-20%. Usuallyit is anonoliguric renal failurewith decreasedGFRand increasedcreatinine andurea. ATNoccurs morefrequently after 7-10 daysfrom the beginning oftherapy (5)(6).

In the case of multidrugpoisonings the substances most frequently involved were: combination of Paracetamol, NSAIDs and Metamizol, followed by

combinations that included substances like: metformin, colchicine, cardiotropic drugslike calcium channel blockers, digoxin and ACE inhibitors, opioids and barbiturates. NSAID sinhibit the production of prostaglandins, thus the effect of catecholamine and angiotens in will not be counteracted, resulting invasoconstriction and decrease drenal blood flow with the development of ischemia and acute tubularnecrosis. Renal injurymay been hanced by dehydration, hypovolemia, or concurrent use of diuretics (7).

In mushroom poisonings, in most cases (17 cases) were involved mushrooms with long incubation period probably Amanita Phalloides, poison ings that usually have associate drenal injury and fulminant hepatic failure. The phaloidiansyndrome is characterized by long incubation over 6 hours and for the practitioner this impliesemergency hospital ization for all patients who have symptoms after this time (8).

Insecticide poisonings included 15 cases and the etiology was represented mainly by organophosphorus insecticides ,Diazinon type, carbamate insecticides Furadantype and less frequently organochlorine insecticides and aluminum phosphate.

The etiology ofalcohol poisoning most commonly included 7 cases of ethylen glycol poisoning followed bymethyl alcohol with 2 cases and by polyethylene glycol with 1 case. The lethal dose infatalethylene glycol poisoning can be appreciated between 1-1.5 ml/ kg. The kidneyis the target organ most frequently affected by ethylene glycolpoisoning. The oxalate, metabolite ofglycolicacid forms precipitates and oxalatecrystalsin the presence ofcalcium. Oxalatecrystals are observed in the renal tubules and can lead to lesionsof interstitial nephritis, focal hemorrhagic necrosis, and acute tubular necrosis especially in theproximal tubule (9,10).

Looking at the severity of renal disease we found that mushroompoisonings were mostsevere, they were associated with AKI stage 3 in 75% of cases, compared to 15% for stage 1, and 10% for stage 2. Instage 3 posioning with pharmaceutical substances was presentin 50% of cases, stage 2 in 33.3% of cases andstage 1 in 16,7%.

c. Clinical and laboratory modifications

Urine output changes begin to occura long with progression of renal injury, oliguria and anuria being more frequent in stage 3 of the AKI compared to stages 1 and 2. In stages 1 and 2 urine out put ispreserved in asignificant proportion of cases. Alsowe can notice that the urine output is preserved alsoina percentage of 16.7% of cases with stage 3 AKI. Oedema ispresent mainly instage 3 of AKI and hypertensionis more commonin stage 3 compared to stage 2 and 1. Also instage 2 we notice the presence of asignificant number of cases with hemorrhagic manifestations, probably explained by the presence of the hepato renal syndrome associated with severe mushroompoisonings. Hepatocytolisis was present in 45 cases, most commonly in the stage 3 AKI – 60% of cases, liver failure defined as prothrombin activity below 50% was seen in 26 cases, more frequently in the stage 3 AKI – 70% of the cases. Among the electrolyte disturbances, hyperkalemia and hyponatremia were present more frequently in stage 3 of AKI and the frequency of acidosis increased with the severity of AKI

d. Estimating the risk of death

On the group of 82 cases studied, 26 deaths were recorded, mortality was 32%. The average length of hospitalization was 10.48 ± 8.1 days well above the average hospitalization time in children's poisoning. The time to onset of AKI was 2.5 ± 2.7 days.

TABLE 1. *Estimating risk of death*

	Deaths	OR	95% Confidence Interval		p-val
Hypertension	7 (35%)	1.21	0.420	3.538	> 0.05
Oliguria	**20 (58.8%)**	**10**	**3.347**	**29.880**	**< 0.05**
Anuria	**7 (63.6%)**	**4.789**	**1.259**	**18.220**	**< 0.05**
Normal diuresis	4 (10.3%)	0.109	0.033	0.360	> 0.05
Hemorrhage	**9 (90%)**	**29.118**	**3.438**	**246.588**	**< 0.05**
Tachypnea	**18 (62.1%)**	**9.205**	**3.182**	**26.625**	**< 0.05**
Edema	**16 (76.2%)**	**16.320**	**4.859**	**54.814**	**< 0.05**
Shock	**(88.9%)**	**24.444**	**2.859**	**208.994**	**< 0.05**
Vomiting	25 (35.2%)	5.435	0.657	44.941	> 0.05
Seizures	9 (50%)	2.765	0.941	8.122	> 0.05
Hepato-cytolisis	**23 (51.1%)**	**11.848**	**3.174**	**44.231**	**< 0.05**
Coma	**23 (50%)**	**11.000**	**2.951**	**40.999**	**< 0.05**
Hepatic failure	**16 (61.5%)**	**7.360**	**2.589**	**20.926**	**< 0.05**

We observed that oliguria, anuria, edema, hemorrhagic manifestations, polypnea, signs of shock, coma, and hepatic hepatocytolisis were risk factors for death in our study. Of these, the most important was represented by the presence of hemorrhagic manifestations that increased the risk of death by about 7.5 times and the presence of signs of shock that increased the risk of death by 6.7 times. Also from the 26 observed deaths 69.2% occurred in stage 3 of AKI, their risk of dying was 1.4 times

higher. Severe metabolic acidosis was present in 94% of cases, the risk of the death of these patients was 14 times higher.

The etiologyof death wasmainly represented bymushroompoisoningsin30.8% of cases, followed bypoisoningswith drugsin23.1% of cases, alcoholsin15.4% of cases, insecticides in 11.5% of cases and in a smaller percentage hydrocarbons, caustics and nitrite poisoning. We determined bylogistic regression the factors with significant impact on the prognosis, they were antidote administration, hemoperfusion, mushroompo isoningand insecticide poisoning.

Out of 82 analyzed poisonings antidote treatment was applied in 23 cases representing 31.7% of the total, we found that from the 26 deaths in the group that received antidote only 4 patients died antidote compared to the 22 patients who did not receive the antidote. The risk of death of those who do not get the antidote is 2.1 times higher than of those who receive the antidote.

The methods of extrarenal epuration or renal replacement treatment were carried out in 41% of cases. They were not protective factors in the study group. 26 patients (31.7%) received hemodialysis and 8 patients (9.8%) recived hemoperfusion. Of the 26 patient that recived hemodialysis 8 died compared to 18 who did not recived hemodialysis. Hemodialysis was performed in 7 cases of poisoning with ethylene glycol, 8 cases of mushroom poisoning, 8 cases of drug poisoning and in 2 cases of insecticide poisoning.

CONCLUSIONS

Acute poisoning cases in children show asignificant increasein recent years inour country (11). Prevalence of toxicrenalinjury in childrenis 1% but prognosis in these casesis of ten severe, mortality is 32%. The cases of toxic acute renal injury and associated risk factors should be identified and diagnosed quickly to establish aprioritized early and effective treatment. AKI is frequently under estimated and under diagnose din children. The pRIFLE diagnostic criteria must be used when evaluating a severe poisoning in children. Judicious use of nephrotoxic drugs with proper hydrationis the most important measure for the preventing the onset of toxic renal injury during hospitalization.

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