Valproic acid-induced acute pancreatitis in pediatric age: case series and review of literature

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SUMMARY: Valproic acid-induced acute pancreatitis in pediatric age: case series and review of literature.

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Valproic acid (VPA) is commonly prescribed medication for epilepsy, migraine and bipolar disorder. Although the common adverse effect associated with VPA are typically benign, less common adverse effect can occur; these include hepatotoxicity, teratogenicity and acute pancreatitis (AP). VPA-induced pancreatitis does not depend on valproic acid serum level and may occur anytime after onset of therapy.

Re-challenge with VPA is dangerous and should be avoided. The diagnosis of VPA-induced pancreatitis seems to be underestimated because of difficulties in determining the causative agent and the need for a retrospective re-evaluation of the causative factor. More of idiopathic pancreatitis should be a drug-induced pancreatitis. We report four cases of VPA-induced AP found in a group of 52 cases of AP in children come to our attention from January 2008 to December 2012. The aim of these reports is to point out our experience about clinical presentation, diagnosis, management, outcome in children with VPA-induced AP and review of literature.

KEY WORDS: Acute pancreatitis - Valproic acid - Pancreatitis in children.

Introduction

International studies have shown a share increase in cases of AP in children: from 5 to 113 cases yearly in the period 1993-1998 (1), an increase from 25 to 45 cases yearly was recorded in a period 1996-2001 with mean age 9,2y and a ratio M/F1:2 (2). As is known the causes of AP in pediatric age are different from those of adult: biliary-pancreatic anomalies, trauma, systemic disease, viral infections and drug toxicity (3). The AP, because its potential gravity with considerable morbidity and mortality, requires proper definition of diagnosis as well as a specialized multidisciplinary approach. In the literature are reported about 500 drugs liable of the onset of AP. An audit carried out in 2005 divided these drugs

into classes according to the number of reports for each drug associated, in case, to re-challenge. The drugs in first class are associated with 20 reports and, at least, one case of re-challenge; those in second class are associated with case report rate between 10-20 with or without re-challenge; all others drugs belong to the third class. VPA, drug used, the last 25 y as on anticonvulsant of choice for the treatment of generalized epileptic seizure belong to the first class (4). Its adverse effect had, the FDA, to approve, in 2000, a warning about the risk, even fatal, of AP in patients both adult and pediatric. During the last decade has shown a greater focus on the causes of AP drug-induced, but unfortunately, the literature on the subject is still lacking and to date, there is no evidence, on the topic, many prospective studies.

Case record

In the period January 2008-December 2012 we observed 52 cases of AP in pediatric age, etiology was presented: trauma (18%), drug adverse reaction (13,5%), biliary (14%), viral infection (28%) anticholinesterase insecticides toxicity (0,5%), Kawasaki disease (0,5%) no cause identified (23,4%). Gullo Syn-

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drome (3,1%) (5) of seven cases drug-induced, four, 3M and 1F, mean age 7,5 with age range 4-11, are attributable to children taking valproate: two for myoclonic syndrome, one for lennox-Gastaut and the last for focal epilepsy. No children taking others drugs in combination. Plasma level of VPA was within the therapeutic range (350-800 micromol/L), the drug dose taken was between 15-30mg/Kg pro die. The symptoms were represented by abdominal pain with atypical localization; in all cases were present tenseness and meteorism of abdomen, soreness to palpation, absence of peristalsis, Blumberg++ with signs of peritoneal irritation. In one case it was present lethargy, in 3 cases vomiting and in two cases fever. In all cases, at onset of disease, were performed routine and specific tests (amylase, lipase, PCR, APT, procalcitonine) and abdominal ultrasound. At the admission in Emergency Department, only for patients with elevated prognostic score, and after 48 hours for all patients, a TC was performed; in cases with indication, at s-CPRMN. In all cases was made to search of mutations in the genes PRSS1, CFTR, SPINK1 (6). As imaging score we used Balthazar classification (7) and Balthazar Severity Index Score (8). As a prognostic biochemical index we used PCR, TPA, IL-6, procalcitonine and the Pediatric Score for AP of De Banto (9), while considering the valid of APACHE2, which is however, a complex system to be applied outside the IUC. We didn't have need to use ERCP and in one case we have used EUS. A marked leucocytosis with neutrofilia (16-23000) was present in all cases, in three cases hypocalcemia was present (<8); plasmatic level of amylase and lipase were elevated in all cases, at least, three times the baseline value with a prevalence of hyperlipasemia. PCR was elevated (>120mg/L) in two cases PAT in one case and in no case procalcitonine and IL-6. The Pediatric score of De Banto was indicative for SAP (severe acute pancreatitis) in two cases confirmed, at 48 hours, only in one case. No genetic mutations for Cystic Fibrosis or Chronic Pancreatitis was highlighted. The imaging with US, EUS and s-CPRMN revealed no alterations in the biliary tree nor of pancreas and its ducts. In the case of SAP, a subsequent RMN examination showed the evolution of fluid peripancreatic collection in pancreatic pseudocysts. All children were suspended the VPA dose, replaced with Phenobarbital. Medical treatment consisted: TPN, fluid-therapy (early aggressive intravenous hydration in the first 24-48 hours), electrolytic balance, Gabesate-mesilate drip continuous infusion, antibiotic prophylaxis (carbenicim+quinolonic, associated with Metronidazole in two cases in which the prognostic scores were predictive for SAP) and inhibitor proton pump. No surgery cases in one case TC guided drainage, associated with octreotide therapy, of the pancreatic pseudocyst, which resolved with healing after 12 weeks. Discharged, healthy, the others three cases.

No re-challenge, and replacement of VPA with Lamotrigina in one case and Leviracetam in the other cases.

Discussion

The association between VPA and AP in childhood has been detected, for the first time, in a child 8 years old affected by absence seizures (10). In other articles have been published on this theme, followed by numerous reports (11-14) and case control to establish, certainly, that VPA may cause the AP (15). Some authors have suggested that the problem of the risk AP VPA-induced may be more common than thought, pointing out that the risk increases after the first year of therapy and that its suspension causes a resolution of the symptoms (16). Grauso's studies (12) suggest that in the children taking VPA, atypical abdominal pain, lethargy or flu-like syndrome should be considered as symptoms related to AP, recommending so the more detailed diagnosis. The same study pointed out that all cases reports about this question were published, in mostly, in Gastroenterology Journals and, only 8 cases published in Pediatric Journal, for which neurologists and pediatricians may not be informed. The AP drug-induced is rare in pediatric age, but it is one that arouses most interest in the scientific debate about the etiology of the AP in children as well as adult. In case of AP VPA-induced the relationship between the drug and the pathology has long been considered defined, because, the VPA have shown, for the first time, a iatrogenic etiology among the causes of AP (10). The incidence of the AP drug-induced considered, until recently, less 2%, actually, may have been underestimated which can reach values up to four times (17); whereby, before a defining as idiopathic AP it's necessary to exclude the drug liability. Taking into account, however, that others authors, in not recent time, reported cases of hyperamylasemia in patients, receiving VPA, without clinical picture of AP (18), in their series 20% of the 61 cases had hyperamylasemia and only one case, after one year follow-up, developed an AP (19); in another study, 32 (23%) of 134 patients taking VPA had hyperamylasemia and no one of these had an AP (20, 21). There isn't published information on serum lipase level in patients receiving VPA. Thus, it is important that in a patients receiving VPA, the diagnosis of pancreatitis not be based on the finding of an elevated serum amylase level without a compatible clinical picture. Not having certain criteria pathogenetic in the causal relationship between VPA and AP and should be excluded, especially in children, those benign or pathological syndromes linked to pancreatic problems by resorting to investigations of second level means to exclude genetic causes (cystic fibrosis, chronic pancreatitis) be-

nign pancreatic hyperenzimemia (Gullo) or extrapancreatic (macroamylasemia) origin. Resorting, also, to imaging studies (CT, RMN, ERCP, EUS) means to exclude anatomic causes of AP (biliary or pancreatic ducts abnormalities).

Conclusion

VPA-induced pancreatitis does not depend on valproate serum level and may occur any time after the onset of therapy. VPA is commonly prescribed medication for epilepsy, migraine and bipolar disorders. The common adverse effect due to VPA are typically benign, but, less common more serious adverse effect can occur among them, also, AP with, possible, lethal effects. Re-challenge with VPA is dangerous and should be avoided. The diagnosis of VPA-induced pancreatitis seems to be underestimated because of the difficulty in determining the

causative agent and the need for a retrospective re-evaluation of the causative factor. More of idiopathic pancreatitis should be drug-induced pancreatitis, but the diagnosis of drug-induced pancreatitis can be formulated by exclusion, considering all the causes which may give rise to pancreatic alterations. The underestimation of AP drug-induced seems to be due to following factors.

Lack of knowledge of the problem (I diagnostic what I know!) seems to be due to non routine dosage of pancreatic enzymes in pediatric age, in emergency room, the appearance of pancreatic pathology after long time from drug exposure. We believe that the study of pancreatic problems, in these cases, must be deepened in etiopathogenetic terms using, in addition to baseline investigations that permit the diagnostic suspicion, even at second level investigations to exclude diseases linked to genetic alterations, hyperenzymemias (benign or pathologic) of pancreatic or extrapancreatic origin and anatomic biliary or pancreatic causes.

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