Int J Legal Med (2004) 118 : 98–100
DOI 10.1007/s00414-003-0414-3

CASE REPORT

H. Pfeiffer · F. U. Weiss · B. Karger · A. Aghdassi
M. M. Lerch · B. Brinkmann

Fatal cerebro-renal oxalosis after appendectomy

Received: 18 September 2003 / Accepted: 21 October 2003 / Published online: 22 November 2003

Abstract A case of a 24-year-old male with fatal cerebro-renal oxalosis assumed to be due to infusions of the sugar surrogate xylitol after appendectomy is reported. The diagnosis was established only after intensive histological investigations following the autopsy. The clinical picture was characterized by an acute seizure, coma and renal failure 2 days after the first xylitol infusion. Death occurred due to cerebral dysregulation as a very rare complication after parenteral administration of xylitol. Subendothelial double refractive calcium oxalate crystals were found in the walls of cerebral blood vessels, in particular in the stem ganglion regions and in the cortical renal tubules. The most common type of primary oxalosis was excluded by sequencing analysis. The young age, the minor surgical intervention and the otherwise unremarkable history are special features of this case. Since the genetic background of xylitol intolerance is still unclear, it is suggested that it should be banned as a sugar surrogate in clinical practice.

Keywords Cerebro-renal oxalosis · Xylitol · Parenteral nutrition

Introduction

Primary oxalosis, or deposition of calcium oxalate (CaOX) crystals in tissues, results from endogenous overproduction of oxalic acid, which is an autosomal recessive disease caused by a defect in glyoxylate metabolism (Reiter and Winter 1979; Leumann and Hoppe 1991). The most common type-1 hyperoxaluria is linked with a deficiency of the liver peroxisomal enzyme alanine glyoxylate aminotransferase (AGT, EC 2.6.1.44), which catalyses the conversion of glyoxylate to glycine. When AGT is absent, glyoxylate is converted mainly to the oxalate which forms insoluble calcium salts that accumulate in the kidneys and other organs resulting in renal failure and systemic oxalosis. The gene AGXT by which AGT is encoded, consists of 11 exons and encodes a 392 amino acid protein. Sequences for the exons and exon/intron boundaries are available from Genbank (accession-Nr.: M61755-6163 and M61833). Up to now a total of about 25 mutations in the AGT gene have been reported in patients with hyperoxaluria (Coulter-Mackie et al. 2001).

Secondary oxalosis is the result of excessive oxalate accumulation because of increased ingestion, increased production, or decreased excretion induced by exogenous factors (Alkhunaizi and Chan 1996). It can occur due to excessive vitamin C administration (Alkhunaizi and Chan 1996; Mashour et al. 2000), ethylene glycol intoxication (Nizze et al. 1997), the use of methoxyflurane narcosis (Aufderheide and Dulth 1971), after ileal resection and in cases of severe ileal diseases (Smith et al. 1972; Dickstein and Frame 1973), and after infusions containing xylitol (Thomas et al. 1972).

During the past 30 years several cases of fatal reactions following xylitol infusion have been reported (Evans et al. 1973; Schultze et al. 1983; Frydl 1987; Bergmann et al. 1991; Heye et al. 1991; Leidig et al. 2001). In all cases the most striking abnormality was the presence of birefringent crystalline material in the tubules of the kidneys. Furthermore, in the brain small birefringent crystals have been observed in the media of small mid-brain arterioles (Thomas et al. 1972). The selective mechanism of the kidneys and the brain is still unclear.

Case history

Two days after a complication-free appendectomy because of an ulcero-phlegmonic appendicitis a 24-year-old man, weight 75 kg, with an otherwise unremarkable history became somnolent and de-

H. Pfeiffer (✉) · B. Karger · B. Brinkmann
Institute of Legal Medicine,
Röntgenstrasse 23, 48149 Münster, Germany
Tel.: +49-251-8355160, Fax: +49-251-8355158,
e-mail: pfeiffh@uni-muenster.de

F. U. Weiss · A. Aghdassi · M. M. Lerch
Division of Gastroenterology and Endocrinology,
Ernst-Moritz-Arndt-Universität, Greifswald, Germany

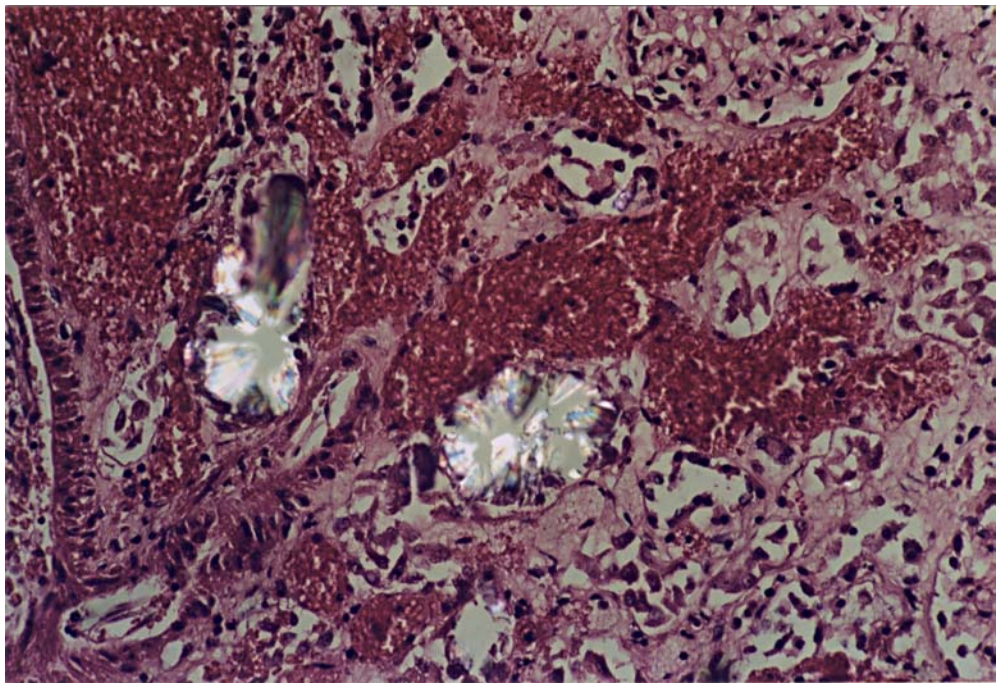

Fig. 1 Secondary renal oxalosis with double refractive calcium oxalate crystals in cortical renal tubules with destruction of the tubulus epithelium surrounded by haemorrhages (HE, 200x, polarised light)

veloped a temperature up to 39°C. Three days after the operation the patient suffered a seizure, fell into a coma, developed acute renal failure and died subsequently of a cerebral dysregulation. Meningitis of unclear genesis was suspected as the cause of death from the clinical point of view. Preoperatively 1000 ml Tutofusin® OP X (Baxter) for parental nutrition was administered. Operatively and postoperatively 2800 ml of the same solution was given and over the following 3 days between 1000 and 2000 ml.

Autopsy findings

A hypoxic-ischaemic damage of the brain with a heavy aqueous swelling of the tissue was found. The operation field was inconspicuous. The other internal organs showed the typical picture of a multi-organ failure. A reason for the death could not be found at the autopsy and microbiological investigations were negative.

Histological findings

Using polarised light microscopy massive depositions of double refractive crystals were found subendothelially in the cerebral blood vessels, in particular in the stem ganglia, and also in the renal tubules. The crystals showed the typical radial structure similar to a rosette. Most of the crystals were located in the tubules of the renal cortex accompanied by necrosis of the tubular epithelium and surrounded by infiltrations of lymphocytes, granulocytes and macrophages. Furthermore in kidney histology the characteristic picture of acute renal failure was found (Fig. 1). The brain tissue showed the picture of a severe hypoxic ischemic damage with a pronounced oedema and nearly complete neuronal necrosis as well as lymphocyte and granulocyte infiltration surrounding the deposits in the walls of the blood vessels. Based on the histological findings, the diagnosis was given as cerebro-renal oxalosis. The cause of death in this case was the oxalosis-induced brain and renal damage.

Molecular genetic investigations

Leukocyte DNA was extracted from an EDTA blood sample using the QIAamp DNA blood kit (Qiagen, Düsseldorf, Germany) according to the manufacturer's protocol. DNA was stored in Tris/EDTA buffer and the exons 1–11 of the AGXT gene were subsequently amplified by PCR using mono-specific oligonucleotide primers. For sequencing of all exons, the Perkin Elmer Big Dye sequencing kit and an ABI Prism 7700 Sequencer were used.

Sequence analysis of the complete coding region revealed the presence of homozygous AGXT major alleles and no mutations in exon 1–11 were detected; in addition the promotor region was in accordance with the published sequence up to nucleotide 134.

Discussion

A deficiency of alanine glyoxalate aminotransferase does not appear to have caused the oxalosis in the patient reported here since no genetic abnormality was found in the entire coding sequence of the AGXT gene.

Since conditions for primary oxalosis and other causes of secondary oxalosis could not be found in our case, the suspicion was that death from cerebro-renal oxalosis was due to the parenteral application of xylitol.

Tutofusin® OP X (Baxter) contains the sugar surrogate xylitol at a concentration of 50 g in 1000 ml fluid. Thus, 190 g xylitol was infused within the first 24 h and 50–100 g during the following 3 days. The extent of renal oxalosis has been shown to be dose-dependent (Mori and Beppu 1983) but the maximal daily dose of 3 g per kg body weight as recommended by the German Federal Public Health Department (Bundesgesundheitsamt 1990) was not exceeded in this case. Tutofusin® OP X (Baxter) is a common infusion solution with a large consumption (half a million bottles sold per year by the manufacturer:personal communication). According to the manufacturer (Baxter) no other fatal case resulting from Tutofusin® OP X infusions has been published. Therefore fatal cerebro-renal oxalosis caused by Tutofusin® OP X infusions seems to be exceptionally rare.

However, four fatal cases of cerebro-renal oxalosis associated with other infusion solutions containing xylitol have been previously reported in Germany (Schultze et al. 1983; Frydl 1987; Bergmann et al. 1991; Leidig et al. 2001).

Compared to the other German case reports, the special features of this case were the young age of the healthy patient, apart from the fact that he suffered from an acute appendicitis, the minor surgical intervention and the fact that diagnosis was established only after autopsy including intensive histological investigations.

References

Alkhunaizi AM, Chan L (1996) Secondary oxalosis: a cause of delayed recovery of renal function in the setting of acute renal failure. J Am Soc Nephrol 7:2320–2326

Aufderheide AC, Dulth M (1971) Renal tubular calcium oxalate crystal depositon. Arch Pathol 92:162–166

Bergmann M, Silling-Engelhardt G, Schnabel R, Gulotta F (1991) Therapiebedingte zerebro-renale Oxalose? Z Ges Inn Med 46: 101–106

Bundesgesundheitsamt (1990) Fruktoseintoleranz und Dosierungsrichtlinien für Kohlenhydratinfusionen. Bekanntmachung über die Zulassung von Infusionslösungen, pp 2–9

Coulter-Mackie MB, Rumsby G, Applegarth DA, Toone JR (2001) Three novel deletions in the alanine:glyoxylate aminotransferase gene of three patients with type 1 hyperoxaluria. Mol Genet Metabol 74:314–321

Dickstein SS, Frame B (1973) Urinary tract calculi after intestinal shunt operation for the treatment of obesity. Surg Gynaecol Obstet 136:257–260

Evans GW, Phillips G, Mukherjee TM, Snow MR, Lawrence JR, Thomas DW (1973) Identification of crystal deposited in brain and kidney after xylitol administration by biochemical, histochemical, and electron diffraction methods. J Clin Pathol 26: 32–36

Frydl V (1987) Zerebrorenale Oxalose – eine metabolische Entgleisung bei parenteralen Infusionen mit Zuckeraustauschstoffen. Zentralbl Allg Pathol Pathol Anat 133:369–376

Heye N, Zimmer C, Terstegge K, Sirtl C, Cervos-Navarro J (1991) Oxalate-induced encephalitis after infusions of sugar surrogates. Intensive Care Med 17:432–434

Leidig P, Gerding W, Arns W, Ortmann M (2001) Renale Oxalose mit Niereninsuffizienz nach Xylitinfusion. Dtsch Med Wochenschr 126:1357–1360

Leumann E, Hoppe B (1991) The primary hyperoxalurias. J Am Soc Nephrol 12:1986–1993

Mashour S, Turner JF Jr, Merrell R (2000) Acute renal failure, oxalosis, and vitamin C supplementation – A case report and review of the literature. Chest 118:561–563

Mori S, Beppu T (1983) Secondary renal oxalosis. A statistical analysis of its possible causes. Acta Pathol Jpn 33:661–669

Nizze H, Schwabbauer P, Brachwitz C, Lange H (1997) Tödliche chronische Oxalose nach sublethaler Äthylenglykolvergiftung. Pathologe 18:328–334

Reiter C, Winter RE (1979) Oxalose: Die forensische Bedeutung von Oxalatkristallen in Geweben. Beitr Gerichtl Med 38:441–449

Schultze G, Pommer W, Offermann G, Molzahn M, Butz M, Krause PH, Lobeck H, Tschöpe W (1983) Akutes Nierenversagen bei sekundärer renaler Oxalose. Weitere Hinweise auf ursächlichen Zusammenhang mit Xylitinfusion. Infusionstherapie 10:322–328

Smith LH, From H, Hoffmann AF (1972) Aquired hyperoxaluria, nephrolithiasis and intestinal disease: description of new symptoms. New Engl J Med 266:1371–1375

Thomas DW, Edwards JB, Gilligan JE, Lawrence JR, Edwards RG (1972) Complications following intravenous administration of solutions containing xylitol. Med J Aust 1:1238–1246