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CLINICAL CASE

Severe acute pancreatitis secondary to hypertriglyceridemia as the onset of Type 1 Diabetes Mellitus in the pediatric age

Pancreatitis aguda grave secundaria a hipertrigliceridemia como debut de Diabetes Mellitus Tipo 1 en edad pediátrica

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What do we know about the subject matter of this study?

Hypertriglyceridemia-induced acute pancreatitis secondary to insulin deficiency in the context of type 1 diabetes mellitus onset is a rare but serious complication in children.

What does this study contribute to what is already known?

The presence of severe hypertriglyceridemia in pediatrics requires considering not only its primary causes but also infrequent secondary causes such as insulin deficiency that occurs at the onset of type 1 diabetes mellitus. Recognition of its etiology and timely management represent a challenge in clinical practice.

Abstract

Hypertriglyceridemia (HTG)-induced acute pancreatitis (AP) secondary to insulin deficiency following the onset of type 1 diabetes mellitus (T1DM) is a rare but serious complication in children. **Objective:** To describe the diagnosis and treatment of severe HTG and to emphasize the need for timely diagnosis of T1DM. **Clinical Case:** A 15-year-old female adolescent with a history of overweight presented with a two-weeks history of fever, anorexia, and diffuse abdominal pain. Laboratory tests revealed triglycerides of 17,580 mg/dL, lipase of 723 U/L, and blood glucose of 200 mg/dL. An abdominal CT scan showed an enlarged and edematous pancreas. She was hospitalized with a diagnosis of AP and severe HTG, which progressed to acute necro-hemorrhagic pancreatitis. Treatment included continuous intravenous insulin infusion until triglyceride levels decreased. Upon discontinuation of insulin, fasting hyperglycemia (206 mg/dL) and metabolic acidosis recurred, therefore DM was

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suspected. Upon targeted questioning, a history of polydipsia, polyuria, and weight loss during the last 3 months stood out. Glycated hemoglobin was markedly elevated (14.7%). Insulin therapy was optimized, achieving stabilization of laboratory parameters after 15 days of treatment and complete anatomical resolution of pancreatic involvement at one year of follow-up. **Conclusions:** The presence of severe HTG in pediatrics compels us to consider its secondary causes, such as the onset of T1DM. It is crucial to improve the ability to diagnose T1DM early, as it may present with infrequent and high-risk presentations for the patient.

Introduction

Hypertriglyceridemia-induced acute pancreatitis (HTG-AP) can occur in the context of severe HTG and the clinical manifestation does not differ from other causes of AP, which is an infrequent secondary complication, with mortality figures in pediatric patients of around 10%[1]. A serum TG level above 1,000 mg/dL (> 11.2 mmol/L) is considered severe HTG[2].

HTG is a metabolic disorder that in children is defined as plasma triglyceride (TG) levels above the 95th percentile for age and sex[3] and can develop as a single lipid disease or as part of a mixed hyperlipidemia. In the United States, the prevalence of HTG, defined as TG > 150 mg/dL (1.7 mmol/L), is approximately 10% among children aged 12 to 19 years[4]. In Chile, a study of 2900 children aged 10-14 years showed that the prevalence of isolated HTG is 9.4%[5]. Depending on its etiology, HTG can be classified as primary, when it is the result of genetic defects in TG synthesis or metabolism, or secondary when it is the consequence of underlying pathology, including obesity, insulin resistance, renal, hepatic, hematologic and endocrine alterations, medications, and uncontrolled diabetes mellitus (DM)[6].

When HTG is associated with obesity, it is usually mild to moderate (130-500 mg/dL [1.47-5.65 mmol/L]). However, when is associated with genetic defects or secondary to diseases or medications, it usually presents as severe HTG[7]. New-onset and uncontrolled type 1 DM (T1DM) and type 2 DM (T2DM) can present with severe HTG, especially in diabetic ketoacidosis (DKA). Elevated TG are explained by excessive lipolysis secondary to lack of insulin effect and the release of free fatty acids from adipose tissue to the liver increases the production of very low-density lipoproteins (VLDL), leading to HTG. In addition, insulin deficiency reduces the activity of lipoprotein lipase in peripheral tissue, which normally hydrolyzes TG into fatty acids and glycerol, and facilitates their entry into adipocytes[4].

A clinical report of severe HTG as a cause of AP in the context of T1DM onset is presented, to describe the diagnosis and treatment of severe HTG and highlight the need for timely diagnosis of T1DM.

Clinical Case

A 15-year-old female adolescent with overweight (BMI/A z-score +1.3 SD), with no other morbid or family history, consulted the emergency department due to unquantified fever, anorexia, and a 2-week diffuse abdominal pain. Initial laboratory tests included a lipid profile with TG levels of 17,580 mg/dL, total cholesterol (TC) 1,633 mg/dL, HDL-cholesterol (HDL-C) 1.8 mg/dL, LDL-cholesterol (LDL-C) 1,573 mg/dL, glycemia 200 mg/dL, lipase 723 U/L, and unprocessed amylase per lipemic sample (table 1).

An abdominal CT scan showed an enlarged and edematous pancreas, without peripancreatic collections (figure 1A). The patient was hospitalized with the diagnosis of severe AP and HTG and continuous intravenous insulin infusion was started. On the third day, a new abdominal CT scan showed signs of hemorrhagic necrotizing pancreatitis.

She was transferred to the Pediatric Intensive Care Unit of the *Hospital Clínico de la Red de Salud UC-Christus* for further management, where she arrived in good general condition, hemodynamically stable, afebrile, and with mild abdominal pain. Physical examination revealed no xanthomas, xanthelasmas, acanthosis nigricans, or hepatomegaly. Control laboratory tests were performed: TG 3,222 mg/dL, TC 887 mg/dL, HDL-C 12 mg/dL, LDL-C 231 mg/dL, glycemia 150 mg/dL, amylase 161 U/L, and lipase 643 U/L (table 1).

Given the persistence of TG over 1000 mg/dL (> 11.2 mmol/L), it was decided to maintain continuous intravenous insulin infusion at 0.05 U/kg/hour, with a glucose load of 2.27 mg/kg/min, and gemfibrozil was started at a dose of 900 mg/day. On day 6, TG dropped to 500 mg/dL (5.6 mmol/L), so continuous intravenous insulin infusion was discontinued. However, the patient evolved with persistent metabolic acidosis, fasting glycemia of 206 mg/dL, and capillary glycemia of 326 mg/dL (table 1). Due to a suspicion of DM and in search of the classic triad of this disease, the patient's medical history was reviewed in a targeted manner, highlighting a history of polydipsia, polyuria, and unobserved weight loss during the last 3 months.

Table 1. Evolution of laboratory samples

Clinical samples	Day 1	Day 2	Day 4	Day 5	Day 6	Day 15	Reference values
Triglycerides (mg/dL)	17,580	4,111	3,222	1,573	519	244	< 150
Total Cholesterol (mg/dL)	1,633	879	887	(-)	434	292	< 200
HDL Cholesterol (mg/dL)	1,8	(-)	12	(-)	(-)	(-)	≥ 60
LDL Cholesterol (mg/dL)	1,573	(-)	231	(-)	(-)	(-)	< 100
Glycemia (mg/dL)	200	(-)	150	206	242	175	< 126
Lipase (U/L)	723	584	643	210	219	73	13-60
Amylase (U/L)	Lipemic*		161	46	25	26	28-100

*A blood sample is considered "lipemic" when it contains an abnormally high amount of lipids or fats. This makes it difficult to properly process the sample in the laboratory.

A glycosylated hemoglobin test (HbA1c) was requested and found to be 14.7% (ref value < 5.7%), along with anti-TPO antibodies < 1, which determined the DM onset before AP. Treatment with insulin (Lantus®) 11 IU/day was started.

On day 10, an abdominal MRI and a cholangiography were performed, which showed images compatible with AP with an acute right anterior pararenal hemorrhagic necrotic collection and another in the transverse mesocolon, with no signs of pancreatic necrosis or gallstones (figure 1B).

Subsequently, insulin therapy was adjusted with an

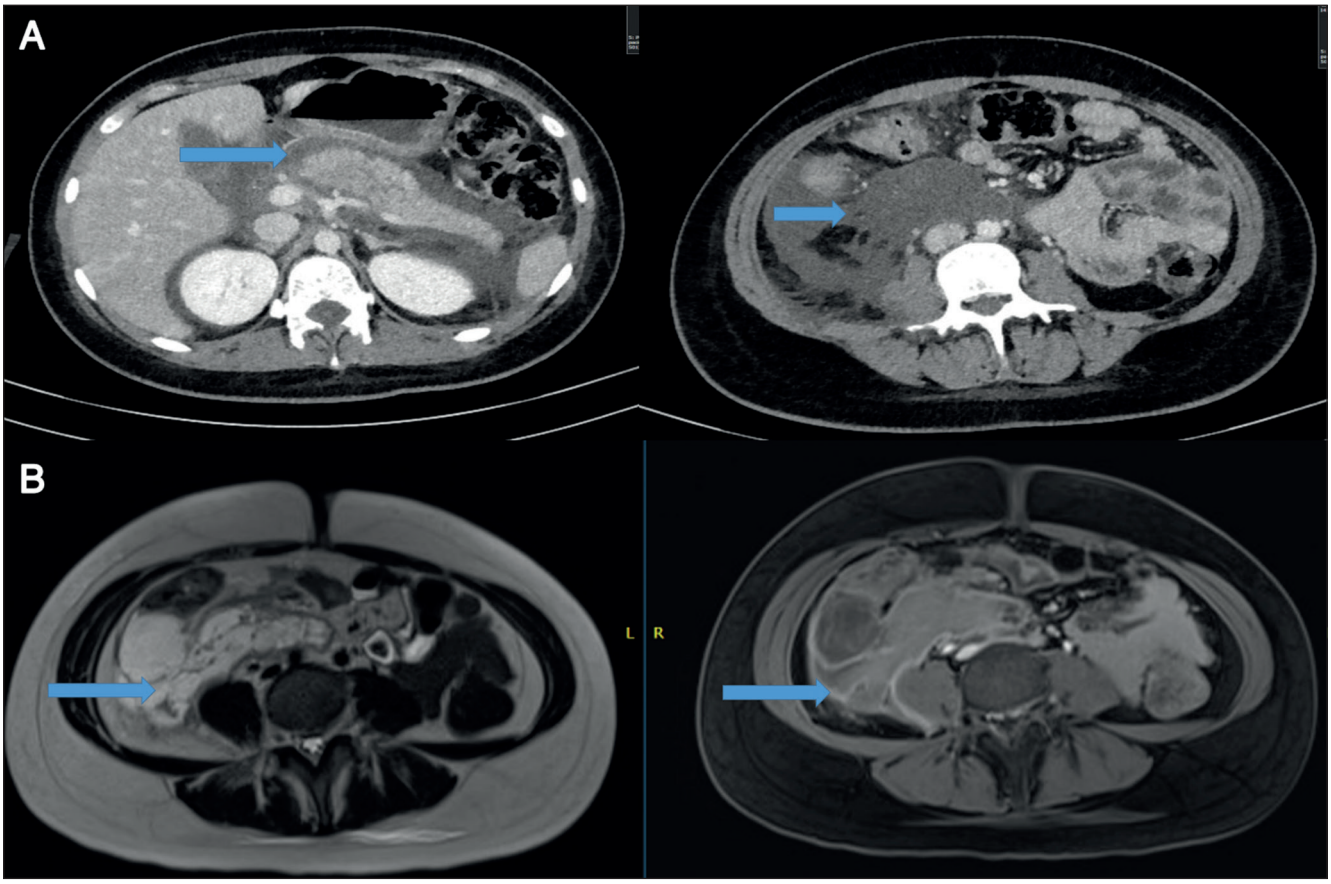

Figure 1. (A) Admission computed tomography (CT), which showed an enlarged and edematous pancreas without peripancreatic collections (arrows). **(B)** Control magnetic resonance imaging (MRI) at 10 days of evolution, which showed AP with an acute right anterior pararenal necrohemorrhagic collection and another in the transverse mesocolon, without signs of pancreatic necrosis or gallstones (arrows).

improvement of metabolic parameters, stabilization of glycemia, and reduction of TG. After 15 days of favorable clinical evolution, without fever or abdominal pain and with good oral tolerance, control laboratory tests showed TG 244 mg/dL, glycemia 175 mg/dL, lipase 73 U/L, and amylase 26 U/L (table 1). Given the improvement of the clinical, laboratory, and imaging findings, hospital discharge was decided.

One month after discharge, outpatient tests were performed and showed normal TG and TC levels, along with good metabolic control because of insulin treatment. Gemfibrozil was discontinued and she continued in follow-up for T1DM. A follow-up abdominal and pelvic CT scan showed a decrease in the size of the anterior pararenal collection and resolution of the collection in the transverse mesocolon. Two months after discharge, a follow-up MRI was performed and showed similar findings to the CT scan, with a decrease in the size of the right anterior pararenal collection. Abdominal ultrasound performed one year after discharge showed complete anatomical resolution of the pancreatic abnormalities.

Discussion

The diagnosis of AP is rare in the pediatric population, with an incidence of 13 cases per 100,000 children[8]. The etiology is diverse in both adult and pediatric age, with infectious and traumatic causes predominating in the latter; however, biliary pathology has become more prevalent[9]. Although HTG and T1DM are described as metabolic causes of AP, they are rare etiologies, so the actual incidence of AP as a complication of T1DM is unknown. However, a study in adults showed that 4% of DKA episodes had AP associated with HTG[10]. AP usually occurs when plasma TG levels exceed 1,000 to 1,500 mg/dL, with a risk of 5% with TG above 1,000 mg/dL (> 11.2 mmol/L), increasing to 20% when the value rises to 2,000 mg/dL (22.4 mmol/L)[7].

Proposed mechanisms of pancreatic injury by HTG include intrapancreatic lipase-induced free fatty acid release with subsequent free radical injury of pancreatic cells, edema, and ischemia, as well as pancreatic ischemia directly induced by capillary hyperviscosity due to hyperchylomicronemia. The triad of HTG, AP, and DKA has been described infrequently and has a complex pathophysiology. The exact role of DKA in the triad remains to be determined, as it is unclear whether it is the cause of AP or rather a complication. Several mechanisms are involved: adipose tissue lipolysis is accelerated by insulin deficiency; lipoprotein lipase inhibition in peripheral tissues leads to decreased VLDL clearance, resulting in HTG and this could also lead to acute βcell dysfunction, increasing transient insulin deficiency and thus favoring DKA[11]. In the case presented, TC and TG normalized after 1.5 months of insulin treatment, indicating that the severe HTG and resulting AP were due to insulin deficiency and not to primary dyslipidemia, which would most likely have persisted despite insulin use[12].

T1DM and the consequent insulin deficiency, both in baseline conditions and in critical situations such as DKA, are associated with elevated TG and cholesterol levels. In this context, it is of utmost importance to improve the diagnostic capacity of health professionals and to educate the general population since the delay in the diagnosis of T1DM is not attributed to the intrinsic difficulty in identifying the disease, but rather to the clarity and ease of recognizing the symptoms, which in general are noticeable and easily identifiable[13]. Early detection of T1DM in children will facilitate the diagnostic process and prevent the development of complications.

One of the therapeutic options for acute HTG associated with abdominal pain or pancreatitis is fasting, which significantly reduces TG in 24-48 hours[6]. When TG reach 1000 mg/dL (> 11.2 mmol/L), a fat-free diet can be initiated if there is no abdominal pain, gradually increasing fat intake to < 10-15% of total calories[6]. Along with fasting, insulin therapy is an effective and safe measure to lower TG more rapidly. Insulin can increase lipoprotein lipase activation, which increases chylomicron clearance, decreasing plasma TG levels[14]. Both intravenous (IV) and subcutaneous administration have been used successfully[15], but continuous IV insulin infusion has the advantage of easier titration. Continuous intravenous insulin infusion (0.1-0.3 IU/kg/h) together with dextrose-saline solution is recommended in non-diabetic patients to maintain euglycemia. Continuous intravenous insulin infusion can decrease TG by 40% and in combination with fasting up to 80% in 24 hours[6]. A retrospective investigation by Ippisch et al. in a pediatric cohort with HTG-AP including 17 patients, showed a statistically significant difference ($p = 0.0339$) in mean TG reduction of 40% with insulin versus 17% without insulin[16].

In refractory cases, plasmapheresis may be an alternative since in adult patients with HTG-AP it has been shown to rapidly reduce TG by up to 70% with only one dose[6]. It is mainly recommended in cases of severe HTG-AP presenting multiorgan failure, exacerbation of systemic inflammation, or presence of lactic acidosis[17]. In the pediatric population, there is a lack of studies on the usefulness of plasmapheresis in these cases, mainly due to the scarce availability of equipment, protocols, and professionals needed to effectively perform therapeutic plasmapheresis to reduce elevated TG levels. Although plasmapheresis can be used

to treat severe HTG, patients with diabetes, such as the one presented in this clinical case, due to the pathophysiology of the disease in general respond rapidly to adequate treatment with insulin.

In adults, fibrates such as gemfibrozil can reduce TG levels by ~45% through stimulation of peripheral lipolysis of triglyceride-rich lipoproteins such as VLDL and chylomicrons by stimulating lipoprotein lipase[18]. Mainly due to their slow mechanism of action, they are not regularly used as monotherapy in the acute management of HTG-AP, although reports are showing that combined therapy with heparin, insulin, and gemfibrozil is safe and effective in rapidly reducing serum triglyceride concentrations in AP associated with HTG[19]. In our case, the use of heparin was not necessary since the patient presented a good response to insulin and fibrates therapy.

Conclusions

The presence of severe HTG in the pediatric population demands careful consideration not only of its primary causes, such as genetic defects in TG synthesis or metabolism but also of secondary causes, including endocrine pathologies, drug use, liver and kidney disease, as well as decompensated T1DM and T2DM.

It is crucial to highlight the need to improve skills in the early diagnosis of DM, which can present with less frequent and high-risk forms of onset for the patient. Delay in diagnosis, as demonstrated by this case, can lead to severe complications, highlighting the importance of recognizing diverse forms of presentation and the need for continuing education for health professionals in the early recognition and timely management of rare associations in the pediatric population.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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References

1. Nydegger A, Heine RG, Ranuh R, et al. Changing incidence of acute pancreatitis: 10-year experience at the Royal Children's Hospital, Melbourne. J Gastroenterol Hepatol. 2007;22(8):1313-6. doi: 10.1111/j.1440-1746.2007.04936.x.
2. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:2969-89. doi: 10.1210/jc.2011-3213.
3. Christensen B, Glueck C, Kwiterovich P, et al. Plasma Cholesterol and Triglyceride Distributions in 13,665 Children and Adolescents: the Prevalence Study of the Lipid Research Clinics Program. Pediatr Res. 1980;14:194-202. doi: 10.1203/00006450-198003000-00004.
4. Valaiyapathi B, Sunil B, Ashraf AP. Approach to Hypertriglyceridemia in the Pediatric Population. Pediatr Rev. 2017;38:424-98. doi: 10.1542/pir.2016-0138.
5. Barja Yáñez S, Arnaiz Gómez P, Villarroel Del Pino L, et al. Dislipidemias en escolares chilenos: Prevalencia y factores asociados. Nutr Hosp. 2015;31:2079-87. doi: 10.3305/nh.2015.31.5.8672.
6. Grisham JM, Tran AH, Ellery K. Hypertriglyceridemia-induced acute pancreatitis in children: A mini-review. Front Pediatr. 2022;10:931336. doi: 10.3389/fped.2022.931336.
7. Scherer J, Singh V, Pitchumoni CS, et al. Issues in Hypertriglyceridemic Pancreatitis: An Update. J Clin Gastroenterol. 2014;48:195-203. doi: 10.1097/01.mcg.0000436438.60145.
8. Uc A, Fishman DS. Pancreatic disorders. Pediatr Clin North Am. 2017;64(3):685-706. doi: 10.1016/j.pcl.2017.01.010.
9. Shukla-Udawatta M, Madani S, Kamat D. An update on pediatric pancreatitis. Pediatr Ann. 2017;46:e207-11. doi: 10.3928/19382359-20170420-01.
10. Nair S, Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: Observations in 100 consecutive episodes of DKA. Am J Gastroenterol. 2000;95:2795-800. doi: 10.1111/j.1572-0241.2000.03188.x.
11. Simons-Linares CR, Jang S, Sanaka M, et al. The triad of diabetes ketoacidosis, hypertriglyceridemia and acute pancreatitis. How does it affect mortality and morbidity?: A 10-year analysis of the National Inpatient Sample. Med (United States). 2019;98:e14378. doi: 10.1097/MD.0000000000014378.
12. Wolfgram PM, MacDonald MJ. Severe hypertriglyceridemia causing acute pancreatitis in a child with new onset type I diabetes mellitus presenting in ketoacidosis. J Pediatr Intensive Care. 2013;77-80. doi: 10.3233/PIC-13053.
13. Hodgson MI, Ossa JC, Velasco N, et al. Cuadro clínico de inicio de la diabetes tipo 1 en el niño. Rev Méd Chile. 2006; 134: 1535-40. doi: 10.4067/s0034-98872006001200007.
14. Eckel RH. Lipoprotein lipase. A multifunctional enzyme relevant to common metabolic diseases. N Engl J Med. 1989;320(16):1060-8. doi: 10.1056/NEJM198904203201607.
15. Mikhail N, Trivedi K, Page C, et al. Treatment of severe hypertriglyceridemia in nondiabetic patients with insulin. Am J Emerg Med. 2005;23(3):415-7. doi: 10.1016/j.ajem.2005.02.036.
16. Ippisch HM, Alfaro-Cruz L, Fei L, et al. Hypertriglyceridemia Induced Pancreatitis: Inpatient Management at a Single Pediatric Institution. Pancreas. 2020;49(3):429-34. doi: 10.1097/MPA.0000000000001505.
17. Garg R, Rustagi T. Management of Hypertriglyceridemia Induced Acute Pancreatitis. Biomed Res Int. 2018;2018:4721357. doi: 10.1155/2018/4721357.
18. Ewald N, Hardt PD, Kloer HU. Severe hypertriglyceridemia and pancreatitis: presentation and management. Curr Opin Lipidol. 2009;20(6):497-504. doi: 10.1097/MOL.0b013e3283319a1d.
19. Hammond DA, Finlay L. Treatment of Hypertriglyceridemia-Induced Acute Pancreatitis With Insulin, Heparin, and Gemfibrozil: A Case Series. Hosp Pharm. 2017;52(10):675-8. doi: 10.1177/0018578717725168.