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Editorial

Inborn errors of metabolism and anesthesia; so far, yet so close☆

Errores innatos del metabolismo y anestesia; tan lejos y sin embargo tan cerca

*Juan Carlos Ibla (MD)**

Associate in Cardiac Anesthesia Children's Heart Institute, Children's National Medical Center, Assistant Professor in Anesthesia and Pediatrics, George Washington University, Washington, DC, United States

The history of Glycogen Storage Diseases (GSDs) begins in the 1920s with the fascinating anatomical description of individuals afflicted by the association of organ hypertrophy and severe metabolic derangements during infancy.[1] The early observations made on this group of patients by Van Creveld, VonGieke and Pompe paved the way for the understanding of a new group of childhood diseases characterized by the inherent inability of "complete glycogen combustion". The body's lack of access to the energy released by the degradation of glycogen led to its accumulation in tissues, in some limited to the liver and kidneys, and in others to the heart and peripheral muscles. Admirably, it was recognized at the time that this was in fact a heterogeneous group of anomalies with complex etiology and no foreseeable treatment. The brilliant conclusions made by these investigators in the early days from such limited information were later corroborated by the discovery of the metabolic steps required in the synthesis and degradation of glycogen.[2]

Today, almost a century later, much is known about the individual enzymatic deficiency of all known GSDs and the metabolic consequences if left untreated. However, the accurate diagnosis of GSDs involves detailed examination of signs and symptoms and the selection of appropriate biochemical and genetic testing. This can be particularly challenging in neonates and young infants in whom the insidious nature of the disease does not provide a clear picture of the exact etiology. In clinical practice, it is routine to evaluate a neonate before surgery in whom a metabolic abnormality is suspected in combination with vague neurological findings or abnormal myocardial function. Even when faced with a confirmed diagnosis of GSD in a neonate and the need for emergent surgery, the question in every anesthetist mind should be: how do I prevent severe complications induced by anesthetics and the metabolic stress of surgery? The answer is not an easy one. Our literature and anesthetic experience with most of GSDs is limited to isolated reports of either severe complications or an "uneventful" course in a wide range of clinical conditions.

For example in the description of John M. Cox, a case series published in 1968, 12 patients (GSD I and III) received general anesthesia, 10 of them for open liver biopsy and 2 for tonsillectomy. While most patients were described to have an uneventful course when receiving cyclopropane, open drop ether or Halothane, one patient (GDSI) suffered cardiac arrest and could not be resuscitated presumably from a ventricular arrhythmia.[3] GSDI or vonGierke's disease is the most common of the GSDs with an annual incidence of 1/50,000 to 100,000 births and manifests itself between 3 and 4 months of age by symptoms of hypoglycemia, tremors, seizures and

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* *Correspondence to*: 111 Michigan Avenue, N.W., Washington, DC 20010, United States.
E-mail address: jibla@cnmc.org

apnea. Normally, glucose-6-phosphatase is a multi-enzymatic system that catalyses the terminal steps of gluconeogenesis and glycogenolysis by converting glucose-6-phosphate to glucose and inorganic phosphate. In GSDI multiple defects in the same enzymatic cascade have been described. For instance, abnormal function of a) glucose-6-phosphate hydrolase (GSD Ia), b) glucose-6-phosphate translocase (GSD Ib), c) translocase for inorganic phosphaste (GCSD Ic) and d) translocase for inorganic glucose (GSD Id) have been diagnosed based on biochemical assays, suggesting that vonGierke's disease is a group of defective enzymatic variants. Interestingly at the genetic level, patients with GSD Ia show mutations in the glucose-6-phosphate hydrolase gene while the rest of GSD I variants (b, c and d) show mutations in the gluscose-6-translocase gene.[4] This highlights the complex biochemical and genetic interaction in GSDs leading to clinically abnormal enzyme function is far from completely understood. As such, the individual response of GSDI variants to general anesthetics will be difficult to predict with any certainty.

A more comprehensive evaluation of the anesthetic effects on patients with GSDs is described for Pompe's disease (GSDII). For this particular GSD, it has been consistently described in the literature the occurrence of ventricular arrhythmias upon induction of general anesthesia with certain anesthetic agents. In the case series presented by Wang et al.[5] from a total of 9 patients undergoing various surgical procedures, patients 1, 4 and 8 in the series experienced ventricular arrhythmias when exposed to different anesthetic agents and did not survive the surgical procedure. The authors suggested that common anesthetic techniques involving propofol or sevoflurane were directly related to the advent of malignant arrhythmias and subsequent patient's demise. This paper also suggests that the preoperative risk stratification for patients with Pompe's disease should involve a detailed assessment of left ventricular mass since patients who died during surgery had the highest indices. Unfortunately, the specific mortality risk for individual anesthetics involved in these cases cannot be calculated based on this information due to the small sample size and the lack of more detailed cardiac physiologic data.

In this edition of the Colombian Journal of Anesthesiology, Valencia et al. present a retrospective study which includes a total of 19 patients and the largest series of patients found in the English literature[6] with GSDIII exposed to common anesthetics. This paper reports no mortality events and only 2 patients experienced any apparent anesthetic related complications. Interestingly, 4 of those patients with GSDIII presented also with some degree of hypertrophic cardiomyopathty; however no ventricular arrhythmias were reported during the anesthetic course. Most patients underwent induction of anesthesia with sevoflurane or propofol and no adverse effects were noted. It was concluded in this paper that the low incidence of complications was in part due to the low risk of surgical procedures in otherwise stable patients.

It is remarkable to learn how much this field of medicine has advanced and our understanding of complex diseases like GSDs continues to grow. The possibility of directed therapy with recombinant human enzymatic replacement for most GSDs is life saving, but certainly raises the bar for the multidisciplinary team caring for these patients. More patients afflicted by rare enzymatic deficiencies will survive longer and the expectations for survival after surgery will increase with advances in technology. We now understand so much more about GSDs, but do we as anesthetists understand the mechanism of anesthetic complications in this group of patients? A good example is the occurrence of ventricular arrhythmias in GSDII versus GSDIII during anesthesia seemingly exposed to similar agents and procedures. It is unclear whether ventricular fibrillation in GSDII patients under anesthesia develops from coronary hypoperfusion, hypoxia, vasoconstriction or if is due to glycogen infiltration of the electrical conducting system of the heart. Are GSDIII patients spared from these effects? In addition, how do patients with GSD and cardiomyopathy compared to patients with isolated cardiomyopathies in their cardiovascular response to myocardial depressing or vasodilator agents? Unfortunately none of this is known and one should anticipate will require the development of dedicated medical centers where centralized care and research converge to provide widely accepted safety guidelines for routine anesthetic care for GSD patients.

In the mean time, for every patient diagnosed with GSD a careful preoperative evaluation and planning should include detail understanding of the heart anatomy and function, careful consideration of anesthetic agents, intraoperative monitoring and post operative management. However, these considerations should apply to every sick pediatric patient with anticipated high morbidity and mortality. In the modern era, we have come so far in the understanding the exact etiology of GSDs, yet we have so much more to learn on how to anesthetize these patients safely and consistently.

Conflicts of interest

The author has no conflicts of interest to declare.

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