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Invited Commentary: Relief for young children with severe chronic pancreatitis

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Lord Moynihan characterized pancreatitis as “illimitable agony” in 1925. (1) Medical and endoscopic management options have improved since then, but remain quite limited. Bellin and colleagues describe a small but important cohort of young children with chronic pancreatitis who underwent total pancreatectomy with islet auto-transplant (TP-IAT) at their center. (2) Chronic pancreatitis is a rare disease in children, but it can cause incredible suffering for the children and families who live with it. Bellin et al.’s group at University of Minnesota has been a leader in TP-IAT for pediatric patients; their experienced insight is an important resource for the pediatric gastroenterology community.

Indications/Patient selection

This case series demonstrates that, though TP-IAT may appear to be a “drastic” step, it offers considerable benefit for the appropriate patient. In adults, TP-IAT is mainly reserved for patients with chronic pain and opioid dependence, but knowledge of the natural history and significance of pancreatitis-triggering genetic mutations in pediatric patients may offer additional consideration with regards to patient selection. Fourteen of Bellin et al.’s 17 children had an identified genetic mutation contributing to their chronic pancreatitis. These included mutations in PRSS1, SPINK1, CTSC, and CFTR. Recent work from the INSPPIRE group, a large multi-center consortium devoted to chronic pancreatitis, reported these genetic mutations in 60% of their cohort (n=301, mean age 11 years). (3) As the work of INSPPIRE and others expand our ability to identify genetic mutations that can trigger pancreatitis, our ability to identify patients that are “doomed” to this chronic condition—and thus that may be appropriate TP-IAT candidates will continue to expand.

We know that early, severe onset of pancreatitis driven by these mutations carries a high risk of chronic pain with opioid dependence and eventual progression to pancreatic exocrine insufficiency and then insulin-dependent diabetes. This cohort’s frequent hospitalizations—a median of 5 per person-year before TP-IAT—supports the severity of disease in these children. In the INSPPIRE cohort, in contrast, children with chronic pancreatitis reported a median of 3 emergency department and 2 hospital admissions per year. (4) For the children and families who live with chronic pancreatitis—and for the health care system—the burden of chronic pancreatitis results in high health care utilization and costs. (5)

Outcomes

Islet auto-transplant, like any allogeneic transplant, should be considered a “trade” of one chronic condition for another. The authors detail potential complications of the surgery, which are important for providers and families considering TP-IAT to understand. Insulin dependence, a calculated risk of TP-IAT, is crucial for families and patients to be counseled about. Other potential complications include portal vein thrombosis, gastroparesis, GJ tube complications, bowel obstruction, bleeding, and infection. Almost one-quarter of this small cohort required re-operation to treat complications, which is significant.

All 17 patients in this Minnesota cohort weaned off of narcotics—which is an important goal post TP-IAT, particularly in children. Only 41% of the cohort were on daily pre-operative narcotics, so this cohort had less opioid dependence than is seen in adolescent and adults. (6) Despite this relatively low rate of daily narcotic use pre-operatively, patients required a median of 2 months to wean off of narcotics. At our center, we have had similar experience that younger children, with shorter duration of disease, often wean off of narcotics more quickly and recover from their chronic pain more easily.

Regardless of opioid dependence, all of these children suffer from chronic pain before TP-IAT. Chronic pancreatitis significantly impairs quality of life in pediatric patients and in their parents. (6) In our experience, psychiatric issues including anxiety, depression, and conversion disorder are common in older children and teenagers suffering from chronic pancreatitis; whether early intervention might alleviate or even prevent these serious morbidities is not known. Close collaboration with pediatric pain specialists is crucial for post-operative pharmacologic and non-pharmacologic pain management, and coping skills. The long-term psychological impact of severe chronic pain, missed school days, disruption of family life has not been systematically studied but should be in the future for these children. Adult studies have shown significant improvements in quality of life after TP-IAT that are independent of insulin dependence; this balance will be important to investigate in children. (7)

Despite the severity of these children’s pancreatitis, they had excellent islet yields—with almost all exceeding the 5,000 islet equivalents per kilogram body mass that has been associated with high prevalence of insulin independence in previous reports. (8) The relatively short duration of disease, and Minnesota’s decades of experience with islet isolation, are both key components of these islet yields.

Following with the high islet yields, insulin independence rates were high—and seemed to be sustained over the reported follow-up period. Reported post-surgical follow-up time was relatively short, with most less than 5 years. Longer-term follow-up of this and other pediatric TP-IAT cohorts will be crucial, particularly in evaluating the sustainability of islets and insulin independence. Even over the relatively short follow-up period, it appears that 3 of the 14 patients that attained temporary insulin independence had to resume insulin. Two of 7 patients that had more than 3 years of follow-up had to restart insulin, and 1 of those 7 never came off of insulin. (1)

Continued monitoring of glucose tolerance, even in those off of insulin, is key for children who undergo TP-IAT. In Bellin et al's cohort, hemoglobin A1c was elevated in 2 patients and borderline elevated in 75% of the cohort. Given their early onset of severe disease, these children would likely have progressed to insulin-dependent diabetes eventually without the TP-IAT. And even their insulin-dependent patients had some islet function, indicated by their C-peptide, which likely gave them some protection from the brittle diabetes that inexorably follows pancreatectomy without IAT. But careful monitoring for hyperglycemia and its consequences—whether or not it reaches the threshold for insulin dependence—will be important for optimizing the long-term health of these children.

Future directions

It is crucial to note that these excellent outcomes were at the highest-volume center for pediatric TP-IAT in the U.S., with the longest-running experience. These outcomes should serve as a benchmark for other programs. The Minnesota group's success in young children speaks to both the center experience and expertise—and to the utility of this surgery for appropriate patients. It also highlights the need for a comprehensive, multi-disciplinary team approach in the pre and post-operative care of these children and their families.

Abbreviations

TP	Total pancreatectomy
IAT	Islet auto-transplant

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