Diabetes Management

Advances in childhood diabetes 2013

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In 1972, a handful of pediatricians met at the Paris home of the pediatrician Henri Lestradet to resolve that henceforth the care and advocacy of childhood diabetes should lie with pediatric specialists, rather than adult diabetologists. In 1974, the first scientific meeting of the then 'International Study Group on Diabetes in Children and Adolescents (ISGD)' took place. The name of the society changed in 1993 to the 'International Society for Pediatric and Adolescent Diabetes (ISPAD)', and in October 2013 more than 1450 specialists in pediatric diabetes from over 80 countries attended the largest ever meeting of ISPAD in Gothenburg, Sweden.

The opening sessions on each day of this 4-day meeting showcased plenary reviews of current issues by international speakers – prevention of childhood diabetes, β-cell replacement, neurocognitive dysfunction and long-term complications. A second plenary on the final day took on the holy grail of insulin therapy – the closed loop.

T Wilkin (Exeter, UK), M Knip (Helsinki, Finland) and A Lernmark (Malmo, Sweden) tackled the issue of prevention in Type 1 diabetes (T1D). Wilkin summarized the emerging – and often controversial – evidence for insulin resistance as the primary driver for T1D, as it is for Type 2 diabetes. The concept is enshrined in the accelerator hypothesis [1], which challenges the primary role of autoimmunity in T1D, and implies that insulin sensitization may prevent the disease where immunomodulation has failed. He announced the first randomized controlled trial to test the role of insulin resistance among children at high-risk for T1D using metformin, to be funded by the Juvenile Diabetes Research Foundation and to start in 2014.

Knip identified the many nutritional factors that associate with a higher risk of T1D – not just calorie excess, but the early introduction of cereals, lack of vitamin D, and lack of ω-3 oils and excess of short-chain amino acids. All, interestingly, are associated with insulin resistance. He went on to summarize the various dietary intervention studies, many of which are too small to draw conclusions, and focused on TRIGR [2], the only properly powered nutritional prevention trial in T1D, which tests whether weaning to an extensively hydrolyzed milk formula prevents the disease.

Lernmark discussed the broader environmental issues in the context of the TEDDY study, a multinational collaboration that is attempting to identify environmental factors that operate at each stage of the disease [3]. He noted that time to onset of disease is related to the number of autoantibodies, and that such markers appear early in childhood if they are going to appear at all. He pointed to the importance of genetic susceptibility, and to the still unknown triggers of the

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immune activity (autoimmunity) that characterizes T1D, and which is believed by many to drive it. The TEDDY study is observing progression in over 8000 births at high genetic risk of T1D, and Lernmark suggested that prevention might be attempted at three different stages – in the genetically susceptible (primary prevention, e.g., hydrolyzed milk formula), in those with persistent islet autoantibodies (secondary prevention, e.g., anti-CD3 monoclonal therapy or the so-called antigen vaccines such as insulin and GAD_{65}) and in those with early disease (tertiary prevention, e.g., β-cell replacement). Observations from TEDDY are providing a rich source of information on the natural history of T1D.

The second plenary took a very different direction, summarizing specific developments in β-cell replacement therapy.

K Le Blanc (Stockholm, Sweden) introduced mesenchymal stem cells (MSCs) as an adjunct to islet cell or β-cell replacement [4]. MSCs exert immunomodulatory properties, and suppress alloreactive donor antihost T-cell responses. They also promote the repair of injured tissue, and have been infused into humans without evident toxicity. No efficacy marker has yet been developed that predicts the clinical response to MSCs, and the ideal conditions for their culture *ex vivo* have yet to be established. Nevertheless, response rates of MSC-treated humans with graft-versus-host response and various autoimmune diseases suggest that they could provide a promising treatment once subjected to proper clinical trials.

The issues surrounding heterologous transplantation are well known to most – rejection, reaction to immunosuppressive drug therapy and recurrence of the insulitis that killed the β cells in the first place. M Bellin (MN, USA) explored current knowledge on autologous islet cell transplantation [5]. Patients undergoing pancreatectomy because of recurrent pancreatitis of the exocrine pancreas have long been saved from diabetes by infusion into the portal vein of their own islets. These autotransplants are not subject to alloimmune rejection, autoimmune recurrence or toxicity to antirejection drugs. Studies of autologous islet transplantation at the University of Minnesota (MN, USA) describe patients who have remained independent of insulin for over a decade, despite having no pancreas. The duration of insulin independency depends on the mass of islets infused and the youth of the recipient. Compared with allografts in diabetic individuals, autografts achieve the same degree of glycemic control with half the mass of islets. These studies show what can be achieved in 'ideal' circumstances where immune tolerance has not been challenged, but it is not clear at this point in time where autologous islets will be sourced for a diabetic patient, nor how the autoimmune reaction can be controlled or the drugs avoided.

Insulin delivery systems have yet to be perfected, and meanwhile people with T1D swing to a greater or lesser extent between extremes of glycemia.

The impact of these fluxes on the developing brain was taken up by T Hershey (MO, USA) who demonstrated the value of neuroimaging [6]. Symptomatically, hypoglycemia can lead to confusion, seizures and altered consciousness, but more subtle dangers lie with long-term cognitive loss, most particularly in children. Hershey summarized the emerging evidence, much of it based on neuroimaging, for cognitive loss associated with extreme swings in blood sugar among young people with diabetes.

Neurocognitive dysfunction in diabetic children is most pronounced in children who develop diabetes during the first 5–7 years of life, and C Ryan (PA, USA) questioned whether it was the result of recurrent hypoglycemia, chronic hyperglycemia or a quite different sequence of events [7]. He presented clinical and nonclinical research to support an 'early events' model, whereby the neurocognitive dysfunction does not develop gradually over time, but is the result of a single insult that occurs around the time of diagnosis, and affects children variably. The model could explain why cognitive loss is apparent within 1–2 years of diagnosis, why there is no progressive deterioration thereafter, and why the degree varies so much between diabetic individuals. The integrity of the blood–brain barrier could be breached in this way by extreme hyperglycemia around the time of diagnosis, or by associated metabolic disturbances such as keto-acidosis.

RJ McCrimmon (Dundee, UK) pointed to research in adults that confirmed that T1D has a relatively specific impact on a subset of cognitive domains, including intelligence, attention, psychomotor speed, cognitive flexibility and visual perception [8]. He reviewed the basic science literature suggesting that the combination of chronic hyperglycemia and recurrent

hypoglycemia was a particularly toxic mix in relation to cognitive dysfunction – one that patients and their doctors should strive to avoid.

The artificial pancreas is of perennial interest to pediatric diabetology, and closing the loop a crucial goal.

M Philip (Petah Tikva, Israel) dealt specifically with nocturnal hypoglycemia, which accounts for 75% of hypoglycemic seizures in children and perhaps 6% of all deaths in patients with T1D. Despite their considerable sophistication in recent years, the risk of hypoglycemia nevertheless remains for all available therapies. To address this challenge, the Diabetes Wireless Artificial Pancreas Consortium (DREAM) was set up with the aim of reducing nocturnal hypoglycemia using the MD-Logic artificial pancreas. The MD-Logic is a fully automated wireless closed-loop system based on fuzzy logic theory algorithms, a personalized system setting and alerts module. Trials on virtual patients using a simulator and on clinical patients in different settings indicate that the system achieves significantly less hypoglycemia and tighter glucose control than either continuous subcutaneous insulin infusion or sensor-augmented pump therapy.

C Acerni (Cambridge, UK) described a series of randomized, controlled studies employing an in-house developed model-predictive control algorithm and standard, commercially available subcutaneous insulin pump and continuous glucose monitoring devices. The studies were part of the APCam research programme aimed at closed-loop delivery systems for patients with T1D [9]. The Florence CL system achieved significant improvements in blood glucose control in young people aged 5–15 years, with reduction in nocturnal hypoglycemia compared with insulin pump therapy alone. The studies have recently extended to the unsupervised home setting.

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