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Endocrinology

Parsing ketotic hypoglycaemia

C A Stanley

Perspective on the paper by Bodamer *et al* (see page 483)

It has been a half century since MacQuarrie called attention to the serious issues of paediatric hypoglycaemia with his presidential address to the American Pediatric Society on “idiopathic hypoglycaemia of infancy”.¹ He pointed out that “idiopathic hypoglycaemia” could lead to seizures or permanent brain damage, and that it might have a genetic basis; however, he speculated that it was unlikely to involve insulin since insulinomas rarely occur in childhood. Over the years, there have been two types of reactions to MacQuarrie’s formulation of “idiopathic hypoglycaemia of infancy”. All too often it has been the ostrich approach of assuming that “idiopathic hypoglycaemia” is a specific entity, forgetting that “idiopathic” is the medicalese equivalent of “I dunno!”. The second type of response has been to search for underlying causes in children labelled as “idiopathic hypoglycaemia”. The latter approach has been much more rewarding, yielding an ever expanding list of new disorders, including genetic defects of hepatic glucose production (for example, deficiencies of fructose-1,6-diphosphatase, glycogen synthase, and the GLUT1 and GLUT2 transporters); a baker’s dozen defects in ketone synthesis and utilisation (for example, deficiencies of medium chain acyl-CoA dehydrogenase, plasma membrane carnitine transporter, and HMG-CoA lyase and synthase); and congenital glycosylation disorders. In addition, contrary to MacQuarrie’s speculation, many cases of “idiopathic hypoglycaemia” have turned out to have one of several genetic disorders of insulin secretion that have been recently elucidated. MacQuarrie’s original familial cases are likely to have had a dominant genetic form of hyperinsulinism. These discoveries have provided a solid foundation for rational diagnosis and management in the majority of infants and children who suffer from hypoglycaemia.

In this issue of the journal, Bodamer *et al* report studies of children with “idiopathic ketotic hypoglycaemia”.² Ketotic hypoglycaemia is, fortunately, part of a shrinking list of disorders that have been hard to rescue from the “idiopathic hypoglycaemia” wastebasket. It was originally described by two investigators from the same institution where MacQuarrie had made his observations on “idiopathic hypoglycaemia of infancy”. Colle and Ulstrom described a group of children who had recurring episodes of hypoglycaemia associated with evidence of ketonaemia and ketonuria.³ The disorder was frequently associated with suspicious past medical histories, such as low birth weight, poor weight gain, and male gender. The fact that these infants were ketotic when hypoglycaemic was appropriately highlighted as evidence that their hypoglycaemia could not be blamed on hyperinsulinism. Most cases presented between 6 months and 4 years of age, could be easily managed simply by avoiding too long an overnight period of fasting, and tended to remit by late childhood.

In studying adaptation to a standard fasting challenge of slightly more than 12 hours, Bodamer *et al* found that “ketotic hypoglycaemic” children were more hypoglycaemic, more ketonaemic, and had lower rates of glucose and amino acid turnover compared to control children. This is reminiscent of the observations by Haymond and colleagues 30 years ago that, during fasting, children with ketotic hypoglycaemia had lower levels of alanine, the major gluconeogenic amino acid, compared to control children.⁴ Both sets of data indicate that hypoglycaemia in children with ketotic hypoglycaemia reflects under-production rather than over-utilisation of glucose.

It is unfortunate that, in the title of their report, Bodamer *et al* perpetuate the

term “idiopathic hypoglycaemia” since “ketotic hypoglycaemia” is more than sufficiently mysterious and ill-defined. One would prefer that “idiopathic hypoglycaemia” would finally be excised from the lexicon of paediatrics, in a manner similar to the outdated term, “nesidioblastosis”. In particular, it is not clear whether children placed in the “ketotic hypoglycaemia” category share a common disorder or represent heterogeneous underlying disorders. Recently, Weinstein and colleagues have suggested that a significant proportion of ketotic hypoglycaemia cases may have a genetic deficiency of glycogen synthase.⁵ Since one of the co-authors of the report by Bodamer *et al*, Professor Leonard, has contributed to the advances in identifying specific defects in hypoglycaemic children over the last several decades, one hopes that the use of “idiopathic” in the title is intended to be tongue in cheek!

There are some problems with how best to interpret the observations of lower levels of gluconeogenic substrate and glucose production in children with ketotic hypoglycaemia in comparison to control children fasted for similar lengths of time. Does this reflect a qualitative or simply a quantitative difference in fasting adaptation? In the study by Bodamer *et al* and in the older studies by Haymond *et al*, ketotic hypoglycaemic children and controls are compared after similar durations of fasting rather than at equivalent physiological stages of fasting. One interpretation of these data is that children with ketotic hypoglycaemia have abbreviated fasting tolerance due to accelerated starvation. The declines in glucose production and amino acid concentrations and the activation of fatty acid oxidation and ketogenesis observed in these children may be perfectly normal, simply occurring earlier than they do in the majority of children. Similar accelerated starvation occurs in lean compared to obese individuals, in adult women compared to adult men, in children compared to adults, and in pregnant and lactating women compared to non-pregnant women. It is possible that children with ketotic hypoglycaemia merely represent the lower end of the bell shaped curve for fasting tolerance in children. Their symptomatic episodes of hypoglycaemia might simply reflect what could occur in other children if the usual overnight period of fasting were 18 instead of 12 hours.

The diagnosis of ketotic hypoglycaemia remains one of exclusion which can only be applied after all other known disorders of fasting homeostasis have been ruled out. In our own experience, we have been impressed that the frequency of this diagnosis has dropped considerably in the past 10–20 years. Does this reflect improvements in our ability to make more specific diagnoses, now that we have a longer list of defined disorders? Alternatively, could it reflect secular changes in pre-natal or peri-natal risk factors for later development of disordered glucose homeostasis? For example, there is currently great interest in the “Barker hypothesis” that

intrauterine fetal growth retardation predisposes to later development of diabetes, obesity, and insulin resistance. Is it possible that “ketotic hypoglycaemia” in some individuals might share in these fetal imprints on future metabolic adaptations? Clearly, children with ketotic hypoglycaemia still present an important puzzle(s) for paediatricians to solve.

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