Annotation

Nesidioblastosis unravelled

What’s in a word? Nesidioblastosis is a word shrouded in confusion because it has been used to mean different things at different times. Gained by Laidlaw in 1938 to describe a diffuse ductoendocrine proliferation of B cells in the pancreas of a patient with a B cell tumour, the word remained a histopathological curiosity until the development of radioimmunoassays in the 1960s led to the recognition of neonatal hyperinsulinaemia hypoglycaemia as an entity. The association of a characteristic clinical picture with hyperinsulinaemic hypoglycaemia focused attention in fatal cases on the pancreas. Nesidioblastosis rapidly acquired a clinical connotation and for a time the word enjoyed vogue as a clinical diagnosis. Subsequent experience has shown that the clinical presentation of neonatal hyperinsulinaemia hypoglycaemia is its most consistent feature and that both the biochemical findings and especially the histopathology are diverse. This led some authors to use clumsier labels such as ‘persistent neonatal hyperinsulinaemic hypoglycaemia (PNHH)’ and ‘persistent hyperinsulinaemia hypoglycaemia of infancy (PHHI)’ to describe the disease, while others now use the term nesidioblastosis either for the clinical condition or to describe a histopathological entity. Hence the confusion. In this review I shall argue that the clinical condition referred to above does not have a single aetiology but arises from convergence of a variety of molecular pathologies. Likewise, the histopathological features we call nesidioblastosis have a spectrum of causes and are no more than a common pancreatic response to precocious growth or regeneration that may occur in human pathology or animal experimentation. In order to unravel nesidioblastosis I have to use the word loosely as a portmanteau term in an account of clinical disease, chemical pathology, histopathology, and their molecular and genetic antecedents.

Clinical features
The patient may be mistaken for the infant of a diabetic mother in being large for gestational age and chubby. Hypoglycaemia is typically symptomatic and may occur in the course of a normal feeding schedule or only if milk is withheld for some hours. A high rate of glucose infusion is needed to maintain normoglycaemia and this may be helpful in alerting diagnostic suspicion in the neonatal period. The diagnosis may be made promptly by an astute clinician or only after other conditions such as certain inborn metabolic errors or Beckwith-Wiedemann syndrome have been excluded. The work of Aynsley-Green et al remains authoritative for those wishing to read about the clinical aspects of nesidioblastosis and its management.

Chemical pathology
Hypoglycaemia and the absence of ketonuria can and should be recognised at the bedside and lead to a prompt request for the determination of plasma insulin concentration. Insulin is measured either during hypoglycaemia or during a formal challenge with an insulin secretagogue. The insulin result may be above the normal range or ‘normal’ yet inappropriately high for the associated blood glucose. This has led to the use of the ratio between glucose and insulin as a biochemical diagnostic index. In such circumstances it is important to have reference figures for infancy from the laboratory making the insulin measurements and not to rely on published data. Alternatively, association of a normal plasma insulin with a pathologically high plasma C peptide permits the diagnosis. The different patterns of abnormal insulin secretion observed in nesidioblastosis suggest that there may be a spectrum of molecular pathologies leading to inappropriate insulin secretion, but this remains to be established.

Histopathology
The reader can find whatever description pleases in the literature on nesidioblastosis and for that reason attention is drawn here to only two papers. Goudswaard et al took the trouble to construct a reference matrix of ‘normal’ pancreatic histology with 49 specimens ranging from fetuses of 15 weeks through the neonatal period, infancy, and up to adulthood. They observed that the histological characteristics of normal fetal pancreas were also found in normal postnatal pancreas and for this reason argued that abnormal endocrine histology should only be diagnosed on the basis of quantitative histometry. When tissue from five cases of nesidioblastosis was compared all parameters were within the normal range. That led to the re-examination of all the remaining pathological tissue and the discovery of islet cell microtumours in three of the five cases. In another
major contribution to the morbid anatomy of nesidioblastosis, Goossens et al made a meticulous study of pancreases from 24 patients diagnosed as having PNHH. They recognised two main forms of histopathological abnormality: diffuse and focal nesidioblastosis. These occurred with equal frequency. Focal nesidioblastosis was characterised by nodular hyperplasia of islet-like cell clusters, including ductoinsular complexes and hypertrophied insulin cells with giant nuclei. Diffuse nesidioblastosis involved the entire pancreas and was distinguished by irregularly sized islets and ductoinsular complexes, both of which contained distinctly hypertrophied insulin cells. Three of the pancreases in the diffuse category were indistinguishable from normal. The reader may reflect on these observations in the context of a pathologist being asked to give an opinion on a frozen section intraoperatively. It is important to emphasise again the diversity of histology associated with abnormal insulin secretion that has caused clinical disease and which usually ends in near total pancreatectomy.

Normal pancreatic development
In a recent review of the developmental biology of the pancreas, Slack pointed out that two distinct cell populations, exocrine and endocrine, arise from endoderm. The early pancreatic bud shows uniform activity of the homeobox gene IPF-1 (also known as IDX-1, STF-1, or PDX) which when mutated to become inactive leads to total absence of the organ. The occurrence of pancreatic heterotopia during development and of metaplasia after regrowth both suggest that only a few gene products distinguish pancreas from the adjacent duodenum, liver, and gall bladder. As the embryonic bud develops endocrine cells differentiate before exocrine cells and early endocrine cells may co-express different hormones (insulin, glucagon, somatostatin and/or pancreatic polypeptide) in the same cell. Although endocrine cells express some gene products that are characteristic of neurones, evidence from in vitro culture and quail-chick chimaeras indicates that they are of endodermal and not neural crest origin. The balance of evidence is that both exocrine and endocrine cells arise from a common stem cell and that a population of these pluripotent stem cells remains in the duct after full development of the gland.

The control of normal proportionality between exocrine and endocrine cells is complex. Suffice here to give three possible mechanisms by which abnormal insulin secretion which could cause hyperinsulinaemic hyperglycaemia of infancy might arise: the defect could be in the B cell, the B cell might be normal yet subject to faulty intercellular signalling that coordinates normal islet function, or there might be an abnormal B cell population quantitatively. The mechanisms proffered are not mutually exclusive. A recent paper by Sanvito et al emphasising the importance of cytokines in pancreatic development is pertinent to the last example. Mouse pancreas was grown in three dimensional gels of extracellular matrix proteins. Collagen gels promoted the formation of acini with relatively poor development of islets, whereas in some basement membrane matrices the development of endocrine cells was dramatically favoured over that of exocrine tissues. Transforming growth factor β1 (TGF-β1) promoted the development of endocrine cells, in particular of insulin containing B cells and of cells expressing genes of the PP (pancreatic polypeptide) family.

The body appears to have no way of sensing the size of the pancreas. The normal pancreas represents a considerable functional excess as seen by the exocrine and endocrine normality of patients who have undergone partial pancreatectomy, in particular infants undergoing 75–95% pancreatectomy for nesidioblastosis. In a paper of practical relevance, Reyes et al examined the proportions of pancreas corresponding to different anatomical landmarks in 13 necropsy specimens taken from children aged 2 days to 15 years. They found pancreatic anatomy to be extremely variable with respect to the fraction of tissue on either side of the superior mesenteric vessels that are the common surgical landmark for a so-called 80% pancreatectomy. The inference is that subtotal pancreatectomy may be less than a surgeon believes. The pancreas has the capacity for regrowth after damage or surgical removal. A number of authors have observed that pancreatic regrowth occurs after pancreatectomy for nesidioblastosis, and while emphasis was placed earlier on the normality of exocrine and endocrine function, attention has been recently drawn to a high incidence of diabetes mellitus and persisting B cell dysfunction at long term follow up.

Experimental nesidioblastosis
Bonner-Weir and Smith have emphasised two pathways by which B cells increase: (a) replication of existing B cells and (b) formation of new islets by proliferation and subsequent differentiation of pancreatic ductal epithelium. The principal stimuli for the replication of existing B cells are glucose, members of the growth hormone family, and some of the peptide growth factors. In contrast, a greater range of stimuli provoke ductal epithelial growth and differentiation. The histology of regenerated pancreas is nesidioblastotic and this may arise clinically as a result of disease or surgery, or experimentally by a number of mechanisms. Examples of clinical nesidioblastotic histology are found after ligation of the pancreatic duct or partial pancreatectomy, recent onset of insulin dependent diabetes mellitus or severe liver disease and, in a recent case report, severe insulin resistance due to a circulating anti-insulin receptor antibody. Experiments resulting in nesidioblastotic histology have included treatment with soybean trypsin inhibitors, wrapping cellophane around the head of the hamster pancreas, or transgenic mice in which interferon G is driven off an insulin promoter. A common feature to all such procedures seems to be the induction of inflammation.

Familial nesidioblastosis
Nesidioblastosis, the clinical disease, was originally considered to be sporadic but review of the literature shows that familial cases have been reported since 1970. While 1988 the condition was recognised, with the name nesidioblastosis, by McKusick as having an autosomal recessive aetiology in some cases. Yagi et al reviewed nine earlier papers in which familial nesidioblastosis occurred 13 times. I have found four more papers and reckon that there are at least 49 instances of familial nesidioblastosis reported in the literature. In societies where consanguinity is prevalent, nesidioblastosis is not a rarity but occurs frequently in some pedigrees. Two papers in 1991 concluded that infantile hyperinsulinaemic hyperglycaemia in general conformed with the distribution characteristics of an autosomal recessive, and Thornton et al are to be credited as the first to suggest that all cases should be regarded as autosomal recessive; they recommend clearly that the parents be advised accordingly concerning the risks of recurrence.

Aetiology of nesidioblastosis
There have been a number of speculations about the aetiology of nesidioblastosis. Brown and Young suggested...
in 1970 that a defect of leucine metabolism stimulated abnormal islet development. At that time 'leucine sensitive hypoglycaemia' was a not uncommon diagnosis, and the matter remains unresolved as to whether leucine is an insulin secretagogue in pancreas that is abnormal for another reason or whether, in some cases, inborn errors of amino acid metabolism might stimulate precocious islet development. A deficiency of somatostatin-containing cells has been noted by two groups. whereas Polak and her colleagues found a lack of somatostatin cells in pancreas from apparently sporadic cases. The question of whether the change in B cell nuclear size was primary or secondary to a loss of mechanisms responsible for B cell function could not be resolved. It seems that an autosomal recessive failure of pancreatic somatostatin cell development remains a plausible explanation for one form of nesidioblastosis. In 1990 Wilkin et al proposed that hyperinsulinaemic hypoglycaemia could come about from islet cell stimulating antibodies. Such an aetiology might apply in later life, but is less likely in the neonatal period. Appreciation that some nesidioblastosis is familial stimulated a hunt for what has been called the PHHI gene. Linkage analysis assigned the gene to chromosome 11p14-15.1 in 1994, which permitted exclusion of some previously mapped genes involved in B cell function from being responsible for this form of nesidioblastosis. These included the glucokinase, islet glucose transporter, and glucagon-like peptide-1 receptor loci. The recent cloning of the gene for the high affinity sulphonylurea receptor (SUR) provided the solution. The SUR gene was mapped to 11p15.1 by means of fluorescence in situ hybridisation and two separate SUR gene splice site mutations, which segregated with disease phenotype, were identified in individuals from nine different families. The SUR gene is a member of the adenosine triphosphate (ATP) binding cassette superfamily and the SUR protein is a putative subunit of the B cell ATP sensitive potassium channel, a modulator of insulin secretion. The authors postulate that the mutations, which involve the most highly conserved region of the gene, lead to disruption of the second nucleotide binding fold and the production of little or no full-length protein, resulting in inappropriately low activity of the potassium channel and resultant insulin secretion. This bald description does scant credit to a most impressive research partnership which involved clinical acumen and perseverance linked to molecular genetic knowhow that has enabled a major advance to be made in our understanding. It is important to appreciate that there is within families with the SUR gene mutation a spectrum of clinical severity in the hypoglycaemia encountered and also in the histopathology of the pancreas.

**Clinical implications**

Discovery of the SUR gene mutation is important, not only because it has brought precision to the analysis of concepts that encouraged lazy thinking from the loose use of the word nesidioblastosis, but because tools will now become available that will permit detection of carriers, of asymptomatic affected individuals, and further analysis of whether apparently sporadic patients may be the index case for a family. The implications for genetic counselling and prevention of further affected infants is self evident. In this way a more complete picture of the spectrum of clinical presentation, biochemistry, and histology that is associated the SUR gene mutation will soon be available.

example, is nesidioblastosis associated with the SUR gene mutation characterised by a consistent pattern of abnormal insulin secretion? What contribution does the SUR gene mutation make to nesidioblastosis overall? Will it be common generally or only in the families so far identified from Eastern Europe and the Middle East? It seems unlikely that mutations of one gene will provide the explanation for all nesidioblastosis, given the complexity of the control of endocrine pancreatic development. Are some of the rare cases of hyperinsulinaemic hypoglycaemia encountered in adulthood forms frustes of infantile nesidioblastosis? Now that a specific genetic defect has been discovered in one form of nesidioblastosis the hunt for other genetic explanations will intensify, especially if families with hyperinsulinaemic hypoglycaemia are identified who clearly have no abnormality of the SUR gene. If an analogy is made with cystic fibrosis, the apparently sporadic occurrence of a rare disease in outbred society may be no more than a reflection of the size of the gene pool and current appreciation that nesidioblastosis is not at all uncommon in consanguineous societies reinforces the hypothesis that all nesidioblastosis is autosomal recessive. I speculate that the SUR gene mutation is but the first of a number of genetic faults which have as a common denominator dysregulation of insulin secretion. Nesidioblastosis unravelled? Maybe not completely, but there are fewer knots to untangle than yesterday.


