Nesidioblastosis

W Zumkeller

University Children's Hospital, Im Neuenheimer Feld 150, 69120 Heidelberg, Germany

(Requests for offprints should be addressed to W Zumkeller, Martin-Luther-University, Halle-Wittenberg, Children's Hospital Medical Centre, Ernst-Grube-Str. 40, 06097 Halle/Saale, Germany)

Introduction

The term 'nesidioblastosis' was originally conceived by Laidlaw (1938) who described the neof ormation of islets of Langerhans from pancreatic duct epithelium whereas 'nesidioblastoma' was proposed for an adenoma composed of islet cells. The term is derived from the Greek words nesidion, for islet, and blastos, for germ. However, only three decades later, severe infantile hypoglycaemia was first associated with nesidioblastosis by Brown & Young (1970). Then, Yakovac et al. (1971) demonstrated the presence of both single islet cells and clusters of islet cells that were separate from the islets of Langerhans in nesidioblastosis. Subsequently, it was suggested that nesidioblastosis may be the result of improper development of the endocrine pancreas progressing beyond birth and neonatal life (Heitz et al. 1977). The advances in molecular genetics have contributed enormously to our understanding of nesidioblastosis or 'unravelled' as outlined elegantly by Professor Milner (1996) in his review.

Hyperinsulinism is the most common cause of persistent neonatal hypoglycaemia. The underlying genetic defects of \( \beta \)-cell regulation include a severe recessive disorder of the sulphonylurea receptor, a milder dominant form of hyperinsulism, and a syndrome of hyperinsulism plus hyperammonaemia. Estimates for the incidence of congenital hyperinsulinaemia vary from 1/40000 live births in northern Europe (Bruining 1990) to 1/2675 live births in Saudi Arabia (Mathew et al. 1988) where consanguineous marriages are common. This condition requires prompt medical and surgical therapy in order to prevent permanent brain damage (Stanley 1997). Nesidioblastosis may also occur in adults (Albers et al. 1989) and it has also been described as a result of coert sulphonylurea administration (Rayman et al. 1984).

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHH), congenital hyperinsulism, nesidiody-splasia and islet-cell dysmaturation syndrome are syno-nyms in use for nesidioblastosis.

Embryology

Both endocrine and exocrine pancreas arise from endodermal buds from which primitive pancreatic ducts and acini develop by repeated branchings (Moore 1993). At birth, increased numbers of islet cells are found throughout the lobule as single cells and as clusters of cells, in addendum to the islets of Langerhans. Nesidioblastosis is found during the first year or two of postnatal life (Van Assche et al. 1970), whereas it does not occur normally in children beyond 2 years of age (Dahms et al. 1980). Nesidioblastosis, resembling third-trimester fetal and neonatal pancreata, has also been found in teratomas of the sacrococcygeal region and anterior mediastinum (Resnick & Manivel 1994). The diffuse pattern of development in the fetal and newborn endocrine pancreas makes the diagnosis of nesidioblastosis therefore rather challenging (Dahms et al. 1980).

Histopathology

The morphologic features characteristic for nesidio-blastosis are ductoendocrine proliferation, numerous small endocrine cell groups and large endocrine areas (Goudswaard et al. 1986). Nesidioblastosis is classified into a focal and a diffuse type which are characterized by different clinical outcomes (Taguchi et al. 1991). Focal nesidioblastosis exhibits nodular hyperplasia of islet-like cell clusters, including ductuloinsular complexes and hypertrophied insulin cells with giant nuclei. In contrast, diffuse nesidioblastosis involves the entire pancreas with irregularly sized islets (Goossens et al. 1989). It was concluded that de novo formation of intermediate cells (acinar-islet cells) is a phenomenon which is clearly associated with nesidioblastosis (Bani et al. 1985). The term 'nesidiodyplasia' has been proposed to include the apparently increased and possibly maldistributed and/or malregulated endocrine cells associated with hyper-insulinaemic hypoglycaemia (Gould et al. 1981). Future classifications will be related to the underlying genetic defects and may thus result in appropriate modification of the existing nomenclature.

A significant increase in total endocrine area of the pancreas with features of widespread infiltration of the acinar tissue by groups of endocrine cells was found by Heitz et al. (1977). In contrast, both Jaffe et al. (1980) and Rahier (1989) observed no such increase. Cultured human islets from an adult with nesidioblastosis showed an increased basal rate of insulin secretion, contained more
Zumkeller: Nesidioblastosis

insulin and had higher levels of insulin mRNA transcripts as compared with controls from normal donors. In addition, autoantibodies against islet cell were found in the serum of a patient with nesidioblastosis (Conge et al. 1997). This occurrence of islet cell surface antibodies has been interpreted as a response to release of islet antigens associated with the proliferative process or, alternatively, it might be that these antibodies have per se a pathogenic role as growth factors (Campbell et al. 1985). These patients should be screened for islet cell autoantibodies and their serum may be incubated with normal islet cells in order to validate this theory.

Progression from nesidioblastosis to pancreatic tumours has been observed in experimental studies. Pancreatic endocrine tumours are rather of hyperplastic than of primarily neoplastic origin (Heitz et al. 1979). Nesidioblastosis is a common feature in insulinoma-associated pancreas as shown both by morphometric and qualitative criteria (Bani Sacchi et al. 1989). The case of an adult patient presenting multiple adenomas of the pancreas with lymph node metastasis, associated with hyperplasia of islets and nesidioblastosis reveals a continuum of proliferative changes (Leong et al. 1980). In fact, wrapping of the pancreas head with cellophane results in the initiation of nesidioblastosis in the Syrian golden hamster (Rosenberg et al. 1983), with reversal of diabetes (Rosenberg et al. 1988). Induction of nesidioblastosis has been shown to enhance pancreatic carcinogenesis in hamsters treated with the carcinogen N-nitrosobis(2-oxopropyl)amine, with the islets being the site of tumour formation (Pour & Kazakoff 1996). A multistep sequence of the development of insulinomas in a Moloney murine sarcoma virus-simian virus-40 (MSV-SV40) large T transgenic mouse model has been postulated which leads from nesidioblastosis to islet cell hyperplasia and dysplasia and finally to tumour formation (Götz et al. 1993).

In contrast to insulinomas and secondary islet hyperplasia due to severe insulin resistance which are positive for islet amyloid (O’Brien et al. 1994), amyloid was undetectable in nesidioblastosis (Rother et al. 1995). However, large numbers of mucopolysaccharide-secreting cells were found in pancreatic nesidioblastosis. Ultrastructural analysis revealed secretion granules and smooth endoplasmatic reticulum containing glycolgen and polysaccharides (Dutrillaux et al. 1979). A novel pituitary protein (7B2) appears to be increased in nesidioblastosis and may be useful as an islet marker (Suzuki et al. 1987), thus facilitating diagnosis.

Pathophysiology

The morphological characteristics of nesidioblastosis have been observed in a number of conditions that do not involve either organic hyperinsulinism or hypoglycaemia, including the Zollinger-Ellison syndrome (Brown & Still 1968), cystic fibrosis (Brown & Mädge 1971), sudden infant death syndrome (Polak & Wigglesworth 1976) as well as normal infants (Dahms et al. 1980, Jaffe et al. 1980, Gould et al. 1983). Non-diabetic children with cystic fibrosis exhibit classic fibrocystic changes of the pancreas and prominent nesidioblastosis (Ianucci et al. 1984). Nesidioblastosis was found in 14 of 38 cystic fibrosis patients with or without diabetes mellitus (Soejima & Landing 1986). Nesidioblastosis has also been observed in patients with α1-proteinase inhibitor deficiency (Ray & Zumwalt 1986).

In a proportion of cases, a significant decrease of pancreatic somatostatin was found in nesidioblastosis (Bishop et al. 1981, Falkmer et al. 1981). An increased ratio of insulin:somatostatin cells was described in several cases of nesidioblastosis, suggesting that a suppression of somatostatin may play a significant role in this disease (Polak & Bloom 1980). Both a deficiency of pancreatic D cells and increased β-cell nuclear size has been found in 15 cases of nesidioblastosis (Rahier et al. 1984). There was, however, no significant change of glucagon and pancreatic polypeptide-secreting cells (Aynsley-Green et al. 1981). Active immunization against glucagon and somatostatin in the rabbit endocrine pancreas has been shown to result in nesidioblastosis (Grube & Jörns 1991). Despite severe β-cell dysfunction, abnormal proinsulin processing appears not to be an intrinsic feature in PHHI (Leibowitz et al. 1996). A role for islet cell-stimulating antibodies for PHHI has been suggested which might apply for adult onset cases (Wilkin et al. 1988, 1990). In these cases, immunologic analysis is warranted in order to elucidate the pathogenetic role of these antibodies.

Genetics

Nesidioblastosis may be sporadic or familial (Moreno et al. 1989, Glaser et al. 1990, Thornton et al. 1991, Bianchi et al. 1992) and autosomal recessive inheritance is most likely (Schwartz et al. 1979, Glaser et al. 1990, Thornton et al. 1991, Woolf et al. 1991, Cherian et al. 1994). Adenomatous hyperplasia of islet cells with nesidioblastosis is also one of the hallmarks of the Beckwith-Wiedemann syndrome in the pancreas (Dahms et al. 1980). Nesidioblastosis was also described in one phenotypic female with Smith-Lemli-Opitz syndrome with a 46,XY karyotype (Lachman et al. 1991). This condition was found in 30% of cases with multiple endocrine neoplasia (MEN) type I (Klöppel et al. 1986, Thompson et al. 1989, Mignon et al. 1993, Le Bodic et al. 1996), occasionally also associated with peliosis (Kovacs et al. 1986). Nesidioblastosis and islet cell carcinoma have been reported in a patient with MEN type I syndrome (Vance et al. 1969). The coexistence of medullary carcinoma of the thyroid and pancreatic nesidioblastosis which may
represent a novel variant of MEN has also been described (Jenkins et al. 1987) and nesidioblastosis has also been reported in a malignant glucagonoma (Bani et al. 1991). The association of nesidioblastosis and congenital neuroblastoma indicates the existence of a 'complex neurocristopathy' (Grotting et al. 1979).

Several strategies were recently envisioned to identify the chromosomal region of the disorder and the gene itself. A homozygosity gene-mapping strategy allowed localization of the disorder to a region on chromosome 11p in five consanguineous families of Saudi Arabian origin (Thomas et al. 1995a). Linkage analysis in 15 families with 29 affected siblings as well as in six families of Ashkenazi Jews mapped familial hyperinsulinism to chromosome 11p14-15.1 (Glaser et al. 1994, 1995). A specific loss of maternal alleles of the imprinted chromosome region 11p15 was observed in cells of the hyperplastic area of the pancreas in cases of focal PHHI, thus providing a molecular explanation of the hetero-geenity of sporadic forms of this disorder (De Lonlay et al. 1997). In a neonate with persistent hypoglycaemia due to hyperinsulinism, the somatic loss of the maternal 11p in an insulin-secreting focal adenoma associated with a germ-line sulpholyurea receptor (SUR1) mutation on the paternal allele has recently been described. Furthermore, it was suggested that focal hyperplasia results from somatic loss of the maternal 11p and that, in addition, a paternally derived SUR1 mutation is a prerequisite for the hyperinsulinism phenotype (Ryan et al. 1998). In four patients with a focal form of PHHI, a reduction to homozygosity of the inherited paternal SUR1 mutation was observed, leading to both β-cell proliferation and hyperinsulinism (Verkarre et al. 1998). De Lonlay et al. (1997) had earlier suggested that islet hyperplasia is either a result of loss of imprinting of the H19 and p57KIP2 genes or of imbalanced expression of H19 and insulin-like growth factor-II (IGF-II). Our own unpublished observation of extremely elevated IGF-II serum levels from a neonate with PHHI due to nesidioblastosis supports this notion.

The high-affinity SUR1 gene was subsequently mapped to 11p15.1 and splice site mutations were detected in affected individuals, indicating that abnormal insulin secretion in PHHI appears to be related to SUR1 mutations (Thomas et al. 1995b). Mutations within the SUR1 gene, which constitutes a subunit of the ATP-sensitive (K<sub>ATP</sub>) channel present in the plasma membrane of pancreatic β cells, have been associated with PHHI in several cases (Aguilar-Bryan & Bryan 1996, Permutt et al. 1996, Meissner et al. 1997). It was also shown that familial hyperinsulinism in Ashkenazi Jews is predominantly associated with mutations in the SUR1 gene (Nestorowicz et al. 1996). In particular, mutations in the first nucleotide-binding fold (NBF1) of the SUR1 gene have been found in PHHI (Thomas et al. 1996b). Absence of K<sub>ATP</sub>-channel activity in PHHI has also previously been shown by patch-clamp studies on islet β cells obtained from affected patients (Dunne et al. 1995, Philipson et al. 1996). It was suggested that the loss of the K<sub>ATP</sub>-channel function removed the intrinsic control of the membrane potential leading to the persistent activation of voltage-dependent calcium channels and unregulated secretion of insulin (Lindley et al. 1996). A mutation in the second nucleotide-binding fold (NBF2) of the sulpholyurea receptor in a patient with PHHI generated K<sub>ATP</sub> channels that could be opened by diazoxide but not metabolic inhibition (Nichols et al. 1996). A mutation in exon 35 of the SUR1 gene has been found to truncate NBF2 and to result in the absence of K<sub>ATP</sub>-channel activity in β cells from a patient with PHHI (Dunne et al. 1997). Structural elements in SUR1 outside the NBFs are also of importance for the regulation of channel activity as revealed by various mutations detectable throughout the molecule (Shyng et al. 1998).

Recently, an activating glucokinase mutation has been identified as a cause of familial hyperinsulinism (Glaser et al. 1998). Furthermore, mutations of the glutamate dehydrogenase gene were identified in children with hyperinsulinism-hyperammonia syndrome (Stanley et al. 1998). Therefore, a number of different gene mutations result in hyperinsulinaemic conditions but associated with different histopathological features.

A homozygous point mutation of the pancreatic islet inward rectifier Kir6.2 was found in the genomic DNA of a child severely affected with PHHI (Thomas et al. 1996b). The K<sub>ATP</sub> channels of β cells comprise two subunits: the high-affinity sulpholyurea receptor SUR1, a member of the ATP-binding cassette superfamily (Aguilar-Bryan et al. 1995) and Kir6.2, a member of the inward rectifier family of potassium channels (Inagaki et al. 1995, Seino et al. 1996). SUR1 is able to couple several types of inward rectifier potassium channels which would imply that mutations in other subunits of the channel may be presented in those affected with PHHI (Ammala et al. 1996). An autosomal dominant form of familial PHHI which appears not to be linked to the sulpholyurea receptor locus has been described in five first cousins of a French-Canadian kindred (Kukuvitis et al. 1997).

A defect in the regulation of nutrient-stimulated insulin secretion pancreatic β-islet cells has been deduced from long-term culture of pancreatic tissue from patients affected with PHHI (Kaiser et al. 1990). An impaired expression of the transcription factor IUF1, which is involved in linking glucose metabolism to insulin regulation as well as in regulating β-cell differentiation, has been described in a β-cell line derived from a patient with nesidioblastosis (Macfarlane et al. 1997). Lack of ATP-sensitive K" channel (K<sub>ATP</sub>) activity was found in a group of five infants with PHHI which resulted in high basal cytosolic Ca<sup>2+</sup> concentrations (Kane et al. 1996).
Symptomatology

Sporadic persistent hyperinsulinaemic hypoglycaemia is a common feature of nesidioblastosis (Aynsley-Green 1981, Aynsley-Green et al. 1981). An inappropriately elevated serum insulin level and low serum ketone and free fatty acid concentrations associated with hypoglycaemia determines the diagnosis (Shilyansky et al. 1997). Arterial calcium injection and subsequent venous sampling reveals a brisk response of the plasma insulin level, indicating that this may be a valuable method for the diagnosis of nesidioblastosis in both children (Abernethy et al. 1998) and adults (Lee et al. 1997). Ultimately, only histological analysis is a valuable tool for the diagnosis of nesidioblastosis.

Treatment

Somatostatin (octreotide) and diazoxide, which is a specific ATP-sensitive potassium channel agonist in normal β cells, are key therapeutics for the treatment of PHHI (Kane et al. 1997). Sulphonylurea drugs are used in diabetes mellitus in order to increase levels of insulin secretion through inhibition of pancreatic β-cell K<sub>ATP</sub> channels (Panten et al. 1992). Kane et al. (1997) suggested that diazoxide may also modulate a novel ion channel in PHHI β cells as they lack K<sub>ATP</sub> currents. Persistent post-operative hyperinsulinaemic hypoglycaemia was successfully treated with the calcium channel blocking agent nifedipine, indicating that ionic control of insulin release in nesidioblastosis may represent a new approach to achieve normoglycaemia (Lindley et al. 1996).

Insulin release from PHHI cells is effectively blocked and blood glucose levels are increased by somatostatin (Otonkoski et al. 1993, Tauber et al. 1994) and, in some patients, pancreatectomy can be avoided with octreotide treatment (Glaser et al. 1993). The side-effects of short- and long-term treatment with octreotide are small and consist in a decrease of linear growth and transient malabsorption in these patients (Thornton et al. 1993). About 40% of children with documented nesidioblastosis had severe neurologic problems (Kaplan et al. 1987) and it is therefore important that octreotide can protect cerebral function and may reduce mortality (Tauber et al. 1994). Baker et al. (1991) suggested that children with PHHI may experience asymptomatic hypoglycaemia which could result in learning difficulties, poor growth of head circumference or show as unspecific signs in an electroencephalogram (Cresto et al. 1998). A regular follow-up should be done in order to prevent neurological dysfunctions.

For infants that are refractory to medical treatment, a 95% pancreatectomy is the treatment of choice (Shilyansky et al. 1997). If symptoms persist after partial pancreatectomy and the patient cannot be controlled with diazoxide or otherwise, total pancreatectomy is required (Kaplan et al. 1987). In adult patients with nesidioblastosis, normoglycaemia has been achieved after subtotal pancreatectomy while receiving diazoxide (Fong et al. 1989). The approach of treatment is, however, different in children with nesidioblastosis. If hypoglycaemia is not controlled by diazoxide or otherwise after 1-2 weeks, surgery is definitely indicated (Warden et al. 1988). The long-term prognosis in patients with nesidioblastosis is related to the extent of the pancreatectomy. The majority of patients who underwent early subtotal pancreatectomy developed insulin-dependent diabetes mellitus during puberty (Leibowitz et al. 1995). Hypoglycaemia is less likely to occur the more of the pancreas is removed. However, the incidence of insulin-dependent diabetes mellitus is far greater. Pancreas function tests indicate subclinical deficiency in patients who had undergone a 95% resection of the pancreas (Cade et al. 1998). Thus, endocrine and exocrine insufficiency remains a continuing risk for these patients.

Concluding remarks

The discovery of gene mutations in patients with nesidioblastosis will help to identify affected individuals as well as carriers, which offers the opportunity for genetic counselling and/or intrauterine diagnosis. Sporadic and familial, neonatal and adult forms may be linked to particular gene mutations. It may be anticipated that there are as yet unidentified gene mutations all resulting in abnormal insulin secretion. Novel therapies may lead to a better outcome and reduce pancreatectomy-associated sequelae. Above all, gene therapy strategies could be devised which would aim to substitute the mutated with the wild-type gene. Greater emphasis should be directed towards the association of nesidioblastosis/insulinoma with MEN type 1. Establishing a link between β-cell hyperplasia and progression to insulinoma will be of utmost importance for understanding pancreas tumorigenesis.

References


Zumkeller: Nesidioblastosis


Laidlaw GF 1938 Nesidioblastoma, the islet cell tumor of the pancreas. American Journal of Pathology 14 125-134.


Lee WL, Won JG, Chiang JH, Hwang JI, Lee CH & Tsay SH 1997 Selective intra-arterial calcium injection in the
Rahier J 1989 Relevance of endocrine pancreas nesidioblastosis to hyperinsulinic hypoglycaemia. *Diabetes Care* 12 164-166.


Endocrine-Related Cancer (1999) 6 421-428
Zumkeller: Nesidioblastosis


