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Genotype-histotype-phenotype correlations in hyperinsulinemic hypoglycemia

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Summary. Hyperinsulinemic hypoglycemia (HH) of pancreatic origin includes congenital hyperinsulinism (CHI), insulinoma, insulinomatosis, and adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia syndrome (NI-PHHS). In this review, we describe the genotype-histotype-phenotype correlations in HH and their therapeutic implications.

CHI can occur from birth or later on in life. Histologically, diffuse CHI shows diffuse beta cell hypertrophy with a few giant nuclei per islet of Langerhans, most frequently caused by loss-of-function mutations in *ABCC8* or *KCNJ11*. Focal CHI is histologically characterized by focal adenomatous hyperplasia consisting of confluent hyperplastic islets, caused by a paternal *ABCC8/KCNJ11* mutation combined with paternal uniparental disomy of 11p15. CHI in Beckwith-Wiedemann syndrome is caused by mosaic changes in the imprinting region 11p15.4-11p15.5, leading to segmental or diffuse overgrowth of endocrine tissue in the pancreas. Morphological mosaicism of pancreatic islets is characterized by occurence of hyperplastic (type 1) islets in one or a few lobules and small, shrunken (type 2) islets. Other rare genetic causes of CHI show less characteristic or unspecific histology.

HH with a predominant adult onset includes insulinomas, which are pancreatic insulin-producing endocrine neoplasms, in some cases with metastatic potential. Insulinomas occur sporadically or as part of multiple endocrine neoplasia type 1 due to *MEN1* mutations. *MAFA* mutations lead histologically to insulinomatosis with insulin-producing neuroendocrine microadenomas or neuroendocrine neoplasms. NI-PHHS is mainly seen in adults and shows slight histological changes in adults and may show slight histological changes, defined by major and minor criteria. The genetic cause is unknown in most cases. The diagnosis of HH, as defined by genetic, histological, and phenotypic features, has important implications for patient management and outcome.

Key words: Congenital hyperinsulinism, Adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia syndrome, Insulinoma, Insulinomatosis, Nesidioblastosis, Mosaicism, Histology, Somatic mutations

Introduction

The term hyperinsulinemic hypoglycemia (HH) covers a broad spectrum of diseases which can be subdivided into primary HH, consisting of congenital hyper-insulinism (CHI), insulinoma, insulinomatosis, and adult-onset non-insulinoma persistent hyper-insulinemic hypoglycemia syndrome (NI-PHHS); and secondary HH, related to maternal diabetes or perinatal stress in neonates, bariatric surgery, medication, autoimmune insulin/receptor disease, and Münchhausen by proxy (Cryer et al., 2009; Thornton et al., 2015).

CHI is a rare, heterogeneous disease with a prevalence of 1:28,000-1:50,000 in the general

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Abbreviations. BCNC, beta cell nuclear crowding; BWS, Beckwith-Wiedemann syndrome; CHI, congenital hyperinsulinism; FAH, focal adenomatous hyperplasia; HH, hyperinsulinemic hypoglycemia; GCK, glucokinase; GDH, glutamate dehydrogenase; GSIS, glucose-stimulated insulin secretion; HK-1, hexokinase 1; IHC, immunohistochemistry; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; NI-PHHS, adult-onset non-insulinoma persistent hyper-insulinemic hypoglycemia; pUPD, paternal uniparental disomy.

population (Yau et al., 2020), with differences in genetics, clinical presentation, histology, and response to treatment. To date, CHI has been associated with mutations in at least 11 different genes: *ABCC8*, *GCK*, *GLUD1*, *HADH*, *HK1*, *HNF1A*, *HNF4A*, *INSR*, *KCNJ11*, *UCP2*, and *SLC16A1* (Rosenfeld et al., 2019; Hewat et al., 2022). CHI may be dominant or recessive inherited, or arise sporadically (Dunne et al., 2004; De Franco et al., 2020). Histologically, CHI is classified into two main well-described forms: diffuse and focal CHI. Other rare histological forms have been described. Histological classification is not possible in approximately 5% of surgically treated patients (Sempoux et al., 2003, 2004; Snider et al., 2013).

Mutations in *ABCC8* and *KCNJ11* on chromosome 11p15.1, encoding the Kir6.2 and SUR1 subunits of the K_{ATP}-channel, are the most common cause of severe CHI and, in large series, have been identified in 36-69% of patients in large series (Kapoor et al., 2013; Snider et al., 2013). Activating mutations in *GLUD1* and *GCK* are the second and third most common mutations in CHI, which lead to increased expression of glutamate dehydrogenase (GDH) and glucokinase (GCK), respectively (Glaser et al., 1998; Stanley et al., 1998; Kapoor et al., 2013; Snider et al., 2013). CHI is a feature of several syndromes, especially Beckwith-Wiedemann syndrome (BWS) and Kabuki syndrome (Kostopoulou et al., 2021; Hewat et al., 2022).

CHI usually develops in the neonatal period and may cause severe and persistent hypoglycemia, or transient forms with spontaneous remission in patients with or without perinatal stress (DeBaun et al., 2000; Kapoor et al., 2008; Kumaran et al., 2010; Stanescu et al., 2012). Rapid diagnosis and treatment are essential to prevent brain injury in both transient and persistent CHI (Avatapalle et al., 2013; Rasmussen et al., 2020b). Advances in the definition of the histological features, molecular genetics, imaging techniques, medical treatment, and surgery have radically changed the management and improved the outcome of patients with CHI, along with a deeper pathophysiological understanding of the various subtypes of CHI.

Insulinoma is a rare cause of HH and is very rare in children with the earliest onset at 3-4 years of age (Boley et al., 1960; Mann et al., 1969; Service et al., 1991; Padidela et al., 2014; Bhatti et al., 2016). This neuroendocrine tumor (NET) can spread locally and metastasize. Insulinomas may present as a part of multiple endocrine neoplasia type 1 (MEN1) syndrome, due to germline pathogenic genetic variants in *MEN1*. Clinical differential diagnoses of insulinoma include insulinomatosis (Anlauf et al., 2009), NI-PHHS (Service et al., 1999), insulin autoimmune syndrome (Church et al., 2018), and secondary causes of HH, such as bariatric surgery (Thompson et al., 2000).

In this review, we focus on the histological features of the different types of HH and their associated genetic changes, clinical characteristics, and treatment with an emphasis on genotype-histotype-phenotype correlations. The following topics will be covered: K_{ATP}-channel diffuse CHI and K_{ATP}-channel focal CHI, GCK-CHI, GDH-CHI, BWS-CHI, mosaic CHI, insulinoma, insulinomatosis, and NI-PHHS. A comprehensive overview of the different entities is shown in Table 1.

Nesidioblastosis

Historically, the term "nesidioblastosis" was linked to HH in neonates and infants (Laidlaw, 1938; Yakovac et al., 1971; Jaffe et al., 1980). Nesidioblastosis is defined as single or small packets of 2-6 beta cells scattered in the walls of small ducts or between acini. This morphological change was later interpreted as a main histological feature of the two major histological forms of CHI, denoted diffuse and focal nesidioblastosis (Goossens et al., 1989). However, nesidioblastosis is present in both diffuse and focal CHI as well as in normoglycemic, age-matched controls (Rahier et al., 1981, 1984; Sempoux et al., 1995; Suchi et al., 2003). Hence, the morphological feature of nesidioblastosis is neither sensitive nor specific for infants with CHI (Rahier et al., 1981, 1984; Sempoux et al., 1995; Suchi et al., 2003). The term nesidioblastosis should, consequently, only be used in its histological meaning and not as the name for a disease entity.

Different forms of hyperinsulinemic hypoglycemia

K_{ATP}-channel diffuse CHI

Genetic and clinical findings of K_{ATP}-channel diffuse CHI

K_{ATP}-channel diffuse CHI is, per definition, associated with biallelic recessive (homozygous or compound heterozygous) or monoallelic dominant loss-of-function (LOF) variants in the K_{ATP}-channel genes *ABCC8* and *KCNJ11* (Kapoor et al., 2013; Snider et al., 2013; De Franco et al., 2020). The homozygous, recessive K_{ATP}-channel mutations are associated with unresponsiveness to diazoxide, which targets SUR1 (Gribble et al., 1997; Shyng et al., 1997; Flanagan et al., 2011a; Rasmussen et al., 2020a). In a large series of patients with diazoxide-unresponsive CHI, 41% had germline mutations in *ABCC8* or *KCNJ11* (Snider et al., 2013). Patients with compound heterozygous pathogenic variants may be responsive to diazoxide (Dekel et al., 2002). Some patients with biallelic K_{ATP}-channel mutations typically have early, neonatal onset of severe CHI with a high risk of neurodevelopmental impairment if not promptly diagnosed and managed (Helleskov et al., 2017; Lord and De Leon-Crutchlow, 2019; Banerjee et al., 2022). Dominant LOF variants usually result in a milder form of diffuse CHI (Huopio et al., 2000; Thornton et al., 2003; Pinney et al., 2008; Kapoor et al., 2011; Oçal et al., 2011). However, the phenotypes overlap and variable responsiveness to diazoxide have been reported for specific variants of *ABCC8* and

KCNJ11, even in transient diffuse CHI (Otonkoski et al., 1999; Thornton et al., 2003; Pinney et al., 2008; Kumaran et al., 2010; Flanagan, et al., 2011b; Kapoor et al., 2011; Macmullen et al., 2011; Oçal et al., 2011; Nessa et al., 2015).

The K_{ATP}-channel LOF mutations disrupt the glucose-stimulated insulin secretion (GSIS) pathway with resultant unregulated hypersecretion of insulin from the beta cells.

Histological findings in K_{ATP}-channel diffuse CHI

In K_{ATP}-channel diffuse CHI, the pancreas does not present gross abnormalities. The number and size of islets are typically normal (Fig. 1A,B). Microscopically, the key finding is beta cell hypertrophy and nuclear enlargement of one or a few single cells per islet of Langerhans (Fig. 1C,D) (Rahier et al., 1984, 1998; Witte et al., 1984; Goossens et al., 1989; Sempoux et al., 1995; Solcia et al., 1997; Sempoux et al., 1998a; Klöppel et al., 1999). Hence, K_{ATP}-channel diffuse CHI is characterized by giant cell nuclei or nucleomegaly (Rahier et al., 1984, 1998; Witte et al., 1984; Goossens et al., 1989; Sempoux et al., 1995, 1998b; Solcia et al., 1997; Klöppel et al., 1999; Han et al., 2016). Nucleomegaly is usually present in 60-70% of islets of Langerhans or more (Rahier et al., 1998; Han et al., 2016).

Morphometric and immunohistochemical studies of K_{ATP}-channel diffuse CHI

Morphometric studies show large beta cells with abundant cytoplasm and abnormally large nuclei of up to 19 µm in diameter, compared with nuclei with a mean diameter of 5-6 µm in normal beta cells. The islets of Langerhans show no endocrine cell proliferation and normal proportions and spatial organization of endocrine cell types (Witte et al., 1984; Goossens et al., 1989; Sempoux et al., 1995; Klöppel et al., 1999). The hypertrophied beta cells with giant nuclei have large

Table 1. Summary of the main histological types of hyperinsulinemic hypoglycemia (HH) and related genotypes and phenotypes.

Type of HH	Pancreatic histology	Genetics	Phenotype*
Diffuse CHI	Nucleomegaly in a few beta cells per islet of Langerhans, distributed throughout the entire pancreas.	Monoallelic or biallelic mutations in *ABCC8* or *KCNJ11*.	Macrosomia from birth. Neonatal onset, persistent HH.
Focal CHI	Focal adenomatous hyperplasia of islets of Langerhans. Size mostly between 2.5 and around 15 mm. Very rare focal extensive forms > 3 cm. Absence of p57/CDKN1C/Kip2 in the lesion.	Paternal monoallelic mutations in *ABCC8* or *KCNJ11*, and somatic loss of maternal 11p15.	Macrosomia from birth. Neonatal onset, persistent HH.
GCK-CHI	Changes range from normal pancreas to increased size of islets, or slightly increased size of nuclei of single beta cells in some islets.	Monoallelic activating mutations in *GCK*.	Neonatal onset HH.
GDH-CHI	A few beta-cell nuclei in a few islets may show a moderate increase in size.	Monoallelic activating mutations in *GLUD1*.	Neonatal or infant onset, persistent HH with mild hyperammonemia.
BWS-CHI	Overgrowth with an increase in the absolute and relative volume of endocrine cells.	Monoallelic mutation in *CDKN1C*. Somatic pUPD, biallelic expression of *IGF2*, and loss-of-expression of *CDKN1C*, *KCNQ1*, *H19*. Epigenetic loss or gain methylation.	Neonatal onset, persistent HH. Macrosomia and mosaic overgrowth defects, increased risk of cancer.
Morphological mosaicism of pancreatic islets	Hyperplastic (type 1) islets confined to one or several adjacent lobules and small, shrunken islets (type 2 islets) distributed throughout the pancreas. Normal expression of p57/CDKN1C/Kip2.	None, or somatic mutations in *GCK*.	Neonatal or infant onset, persistent HH.
Insulinoma	Low-grade NETs, typically WHO grade 1-2. Size typically between 6 and 25 mm. Histological expression of mainly insulin. Neuroendocrine markers, such as chromogranin A and synaptophysin, are strongly expressed.	None, or monoallelic *MEN1* mutations. Variable somatic mutations in *ARHGAP35*, *ATR*, *DOCK4*, *EVA1X*, *FLNC*, *FRG1*, *H3F3A*, *KDM6A*, *LMO2*, *MEN1*, *MLL3*, and *YY1*.	HH onset in late childhood, adolescence, or adulthood. Other MEN1 features are possible.
Insulinomatosis	Multiple insulin-producing neuroendocrine microadenomas (< 5 mm) and/or neuroendocrine neoplasms. Insulin-producing mono-hormonal endocrine cell clusters.	Monoallelic, or biallelic mutations in *MAFA*.	Adult onset HH. Diabetes.
NI-PHHS	No histological changes or multiple beta cells with enlarged and hyperchromatic nuclei and abundant cytoplasm, irregular shape and ocassional enlargement and/or increased number of islets, lobulated islet structure, macronuclei in beta cells.	None, or monoallelic activating *GCK* mutations.	Adult onset HH. Rare cases are seen in adolescence.

*Only typical phenotypes of patients with pancreatic resection (severe CHI) are included. Patients with milder and transient HH phenotypes will not undergo pancreatic resection and hence often have unknown histology. BWS, Beckwith-Wiedemann syndrome; CHI, congenital hyperinsulinism; GCK, glucokinase; GDH, glutamate dehydrogenase; HH, Hyperinsulinemic hypoglycemia; MEN1, multiple endocrine neoplasia type 1; NETs, neuroendocrine tumors; NI-PHHS, adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia syndrome.

Golgi areas indicating hyper-functional activity, supported by high expression of proinsulin. Insulin labeling is, however, very low due to the great uncontrolled hypersecretion of insulin (Klöppel et al., 1999; Rahier et al., 2011).

Treatment of K_{ATP}-channel diffuse CHI

After emergency treatment to correct hypoglycemia, diazoxide is the first-line treatment for diffuse CHI, effective in 50-60% of patients (Salomon-Estebanez et al., 2016; van der Steen et al., 2018; Brar et al., 2020; Lord and De León, 2020). In diazoxide-unresponsive patients, somatostatin agonists may be effective (Arnoux et al., 2010, 2011; Le Quan Sang et al., 2012; Demirbilek et al., 2014; Welters et al., 2015; Salomon-Estebanez et al., 2016; Lord and De León, 2020). Long-acting somatostatin analogs, such as octreotide long-acting release or lanreotide, are increasingly used for the treatment of diffuse CHI (van der Steen et al., 2018; Dastamani et al., 2019).

In case of surgery, leading centers recommend biopsies from the head, body, and tail of the pancreas for intraoperative frozen section analysis to confirm diffuse type CHI before proceeding to subtotal pancreatectomy (Adzick et al., 2019). Subtotal pancreatic resection has been performed and is still being widely used in some centers, but often leads to diabetes and sometimes exocrine pancreatic insufficiency (malabsorption) at long-term follow-up (Lovvorn et al., 1999; Meissner et al., 2003; Beltrand et al., 2012; Arya et al., 2014; Lord et al., 2015; Rasmussen et al., 2020a). This has prompted experimental therapies with other drugs such as sirolimus and nifedipine, which, however, are largely ineffective (Durmaz et al., 2014; Senniappan et al., 2014; Banerjee et al., 2017; Sikimic et al., 2020). More recently, trials with novel drugs such as glucagon analogs, insulin receptor antibodies, and GLP-1 receptor agonists have been conducted (Calabria et al., 2012; Lord and De León, 2020; Sikimic et al., 2020), providing hope for future management.

K_{ATP}-channel focal CHI

Genetic and clinical findings in K_{ATP}-channel focal CHI

K_{ATP}-channel focal CHI is associated with a genetic two-hit etiology with a paternal, recessively inherited heterozygous disease-causing mutation in *ABCC8* or *KCNJ11*, combined with somatic loss of the maternal allele in the 11p15.5 region (de Lonlay et al., 1997; Ryan

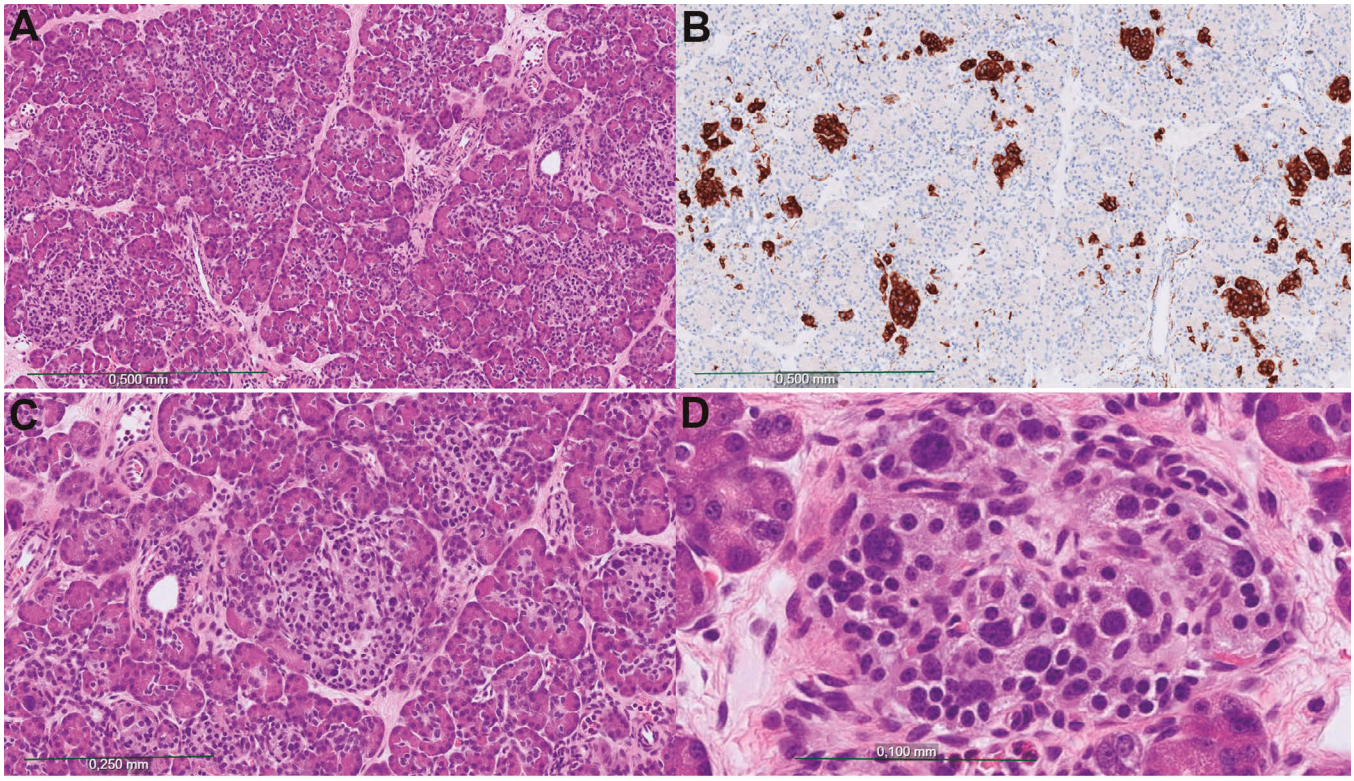

Fig. 1. K_{ATP}-channel diffuse CHI. **A.** The number and size of islets of Langerhans are usually age-appropriate (H&E). **B.** Synaptophysin immunostaining of pancreatic islets is shown. **C.** At medium-power magnification, giant nuclei in beta cells of islets of Langerhans can be observed. **D.** High magnification of an islet of Langerhans with numerous giant nuclei. Scale bars: A, B, D, 500 µm; C, 250 µm.

et al., 1998; Verkarre et al., 1998; de Lonlay-Debeney et al., 1999; Glaser et al., 1999; Fournet et al., 2001; Snider et al., 2013). Somatic mitotic recombination of 11p15.5 results in duplication of the paternal allele leading to homozygosity of the mutated *ABCC8/KCNJ11* locus and paternal uniparental disomy (pUPD) for all genes telomeric to *ABCC8/KCNJ11* (Damaj et al., 2008). In the imprinting region 11p15.5, only the maternal allele expresses the tumor suppressor *CDKN1C* encoding the protein p57 and the long non-coding RNA *H19*, whereas the paternal allele expresses *IGF2* encoding insulin-like growth factor 2 (*IGF2*), which has proliferative and anti-apoptotic effects (Petrik et al., 1998, 1999). The imbalance of expressed growth/tumor suppressor genes leads to focal CHI (de Lonlay et al., 1997; Ryan et al., 1998; Verkarre et al., 1998; Fournet et al., 2001; Damaj et al., 2008). Detailed studies have shown varying recombination breakpoints and upregulation of the growth promoter gene *ASCL2* and other pancreatic transcription factors (Giurgea et al., 2006a; Wieland et al., 2022). The combination of focal overgrowth and hypersecretion of insulin leads to the histological features of K_{ATP}-channel focal CHI. K_{ATP}-channel focal CHI is found in approximately 50% of diazoxide-unresponsive CHI patients, however, with a variable prevalence of 17-65% in different studies (Bellanné-Chantelot et al., 2010; Kapoor et al., 2013; Lord et al., 2013; Snider et al., 2013; Adzick et al., 2019). The positive predictive value of a monoallelic, paternal K_{ATP}-channel mutation in a child with diazoxide-unresponsive CHI is 94% for the diagnosis of focal CHI with a sensitivity of 97%, as *de novo* K_{ATP}-channel mutations on the paternal allele are also observed (Suchi et al., 2006; Snider et al., 2013). K_{ATP}-channel focal CHI presents within the first days of life and is usually, but not always, diazoxide-unresponsive (Ismail et al., 2012; Maiorana et al., 2014). The risk of K_{ATP}-channel focal CHI in the offspring of paternal K_{ATP}-channel mutation carriers has been estimated to 1:540 (Glaser et al., 2011). Consequently, families with more than one child with focal CHI are very rare (Ismail et al., 2011). Likewise, siblings with focal and diffuse CHI are exceedingly rare (Valayannopoulos et al., 2007; Ismail et al., 2011).

Terminology

In the literature of the past 60-70 years, K_{ATP}-channel focal CHI has been referred to by many different names: Congenital islet cell adenoma (Buist et al., 1971), islet cell adenomatosis (Schwartz and Zwiren, 1971), islet-cell adenoma (Baerentsen, 1973), focal islet cell adenomatosis (Klöppel et al., 1975), congenital insulinoma (Carney, 1976), pancreatic adenomas with nesidioblastosis (Dahms et al., 1976), mixed islet-acinar adenomas, (Scully et al., 1978), neonatal islet cell adenoma (Bordi et al., 1982), focal nesidioblastosis (Goossens et al., 1989), focal islet hyperplasia (Stanley, 1997), focal adenoma (Ryan et al., 1998), focal adenomatous hyperplasia (FAH) (Rahier et al., 1998), focal hyperinsulinism (de Lonlay-Debeney et al., 1999), focal islet cell adenomatous hyperplasia (Fournet et al., 2001), focal nodular adenomatosis (Smith et al., 2001), focal adenomatous islet-cell hyperplasia (Crétolle et al., 2002), focal persistent hyperinsulinemic hypoglycemia of infancy (FoPHHI) (Sempoux et al., 2003), focal beta cell hyperfunction (Kaczirek and Niederle, 2004), and focal beta cell hypertrophy and hyperplasia (Ouyang et al., 2011). We prefer the histological term focal adenomatous hyperplasia (of endocrine cells) for the lesion that defines K_{ATP}-channel focal CHI.

Histological and immunohistochemical findings in K_{ATP}-channel focal CHI

Focal CHI can arise anywhere in the pancreas, sometimes protruding from the pancreatic surface, and may even occur in ectopic pancreatic tissue (Jaffe et al., 1982; Goossens et al., 1989; de Lonlay-Debeney et al., 1999; Klöppel et al., 1999; Hussain et al., 2006; De lonlay et al., 2007; Christiansen et al., 2018; Longnecker, 2021). The focal lesion is often macroscopically invisible and impalpable (Rahier et al., 1998; Sempoux et al., 1998b; de Lonlay-Debeney et al., 1999).

Microscopically, focal CHI is characterized by FAH consisting of endocrine cells (Fig. 2A). The lesion is sometimes circular or ellipsoid, measuring from 2.5 to 13 mm, and consists of confluent hyperplastic islets (Fig. 2B-D) (Klöppel et al., 1975; Dahms et al., 1976; Jaffe et al., 1980; Bordi et al., 1982; Goudswaard et al., 1986; Goossens et al., 1989; Solcia et al., 1997; Rahier et al., 1998; Sempoux et al., 1998b; de Lonlay-Debeney et al., 1999; Klöppel et al., 1999; Mohnike et al., 2014; Bendix et al., 2018; Bjarnesen et al., 2021). At their periphery, a thin rim of acinar cells and/or ducts, or strands of connective tissue, are present (Fig. 2D) (Klöppel et al., 1975; Dahms et al., 1976; Shermeta et al., 1980; Bordi et al., 1982; Witte et al., 1984; Goossens et al., 1989; Solcia et al., 1997; Rahier et al., 1998; de Lonlay-Debeney et al., 1999; Klöppel et al., 1999; Sempoux et al., 2003).

The limits of the focal lesions are sometimes ill-defined (Klöppel et al., 1975; Dahms et al., 1980; Klöppel and Heitz, 1984; Witte et al., 1984; Goossens et al., 1989; Solcia et al., 1997; Sempoux et al., 2003), however, a lobular structure of the area in the pancreas harboring them is maintained (Rahier et al., 1998; de Lonlay-Debeney et al., 1999; Sempoux et al., 2003).

Cragie et al. observed differences at the periphery of the lesions in a study of 25 surgical specimens (Craigie et al., 2018). In 28% of the cases, the focal lesion projected into adjoining normal pancreatic tissue without clear delineation from normal tissue. In these cases, severe hypoglycemia was detected within a few days following birth. In the remaining patients, the FAH was encapsulated within a defined matrix capsule. These findings remain to be confirmed by others. Occasionally, multiple adjacent lobules are involved (Delonlay et al.,

2007). Like normal islets of Langerhans, beta cells comprise the main endocrine cell type in focal CHI, but at their periphery, also alpha, delta, and gamma cells are found (Dahms et al., 1980; Goossens et al., 1989; Rahier et al., 1998; Klöppel et al., 1999; Sempoux et al., 2003).

Morphometric and immunohistochemical studies of K_{ATP}-channel focal CHI

Early investigations by morphometry and immunohistochemistry (IHC) revealed the presence of alpha, beta, delta, and gamma cells within the lesion (Jaffe et al., 1980; Bordi et al., 1982; Klöppel and Heitz, 1984; Witte et al., 1984; Goossens et al., 1991; Solcia et al., 1997; Sempoux et al., 2003). About 80-90% of cells, including hypertrophied cells, are beta cells (Fig. 2B) (Klöppel et al., 1975; Jaffe et al., 1982; Witte et al., 1984; Goossens et al., 1989; Solcia et al., 1997). In normal infants, the beta cell population accounts for ~50%, alpha cells for ~20%, and delta cells for ~30% (Fig. 2C) (Rahier et al., 1981; Stefan et al., 1983).

Nucleomegaly was quantified in FAH with high-content analysis of the volume of the nuclei using transmission electron microscopy data (Han et al., 2016). Nucleomegaly was sometimes present, but eight times less frequently compared with diffuse CHI (Han et al., 2016), in keeping with previous findings of a lower frequency of large nuclei in focal vs. diffuse CHI (Rahier et al., 1998; Sempoux et al., 1998b).

Sempoux et al. used IHC double staining of the cellular proliferation marker Ki67 and insulin for measuring the mean beta cell labeling index, defined as the number of Ki67 labeled beta cell nuclei per 1000 beta cell nuclei. The mean beta cell labeling index was four times higher in the focal lesion compared with islets of Langerhans in age-matched controls (Sempoux et al., 1998a). A similar beta cell proliferation rate study was performed by Kassem et al. with almost identical results (Kassem et al., 2000). The maternally expressed protein cyclin-dependent kinase inhibitor 1C (CDKN1C), also known as p57 or Kip2, is consistently absent in the FAH, following the pUPD genetic changes in the lesion (Kassem et al., 2001; Sempoux et al., 2003; Suchi et al., 2006; Mohnike et al., 2014).

SUR1, encoded by *ABCC8*, is expressed significantly less on the beta cell surface in focal CHI compared with endocrine cells outside the lesion (Sempoux et al., 2003), compatible with the variable failure of mutated K_{ATP}-channels to either synthesize, mature, assemble, traffick, or reach the beta cell surface (Dunne et al., 2004). IHC double staining of proinsulin and insulin revealed that the hyper-functional beta cells

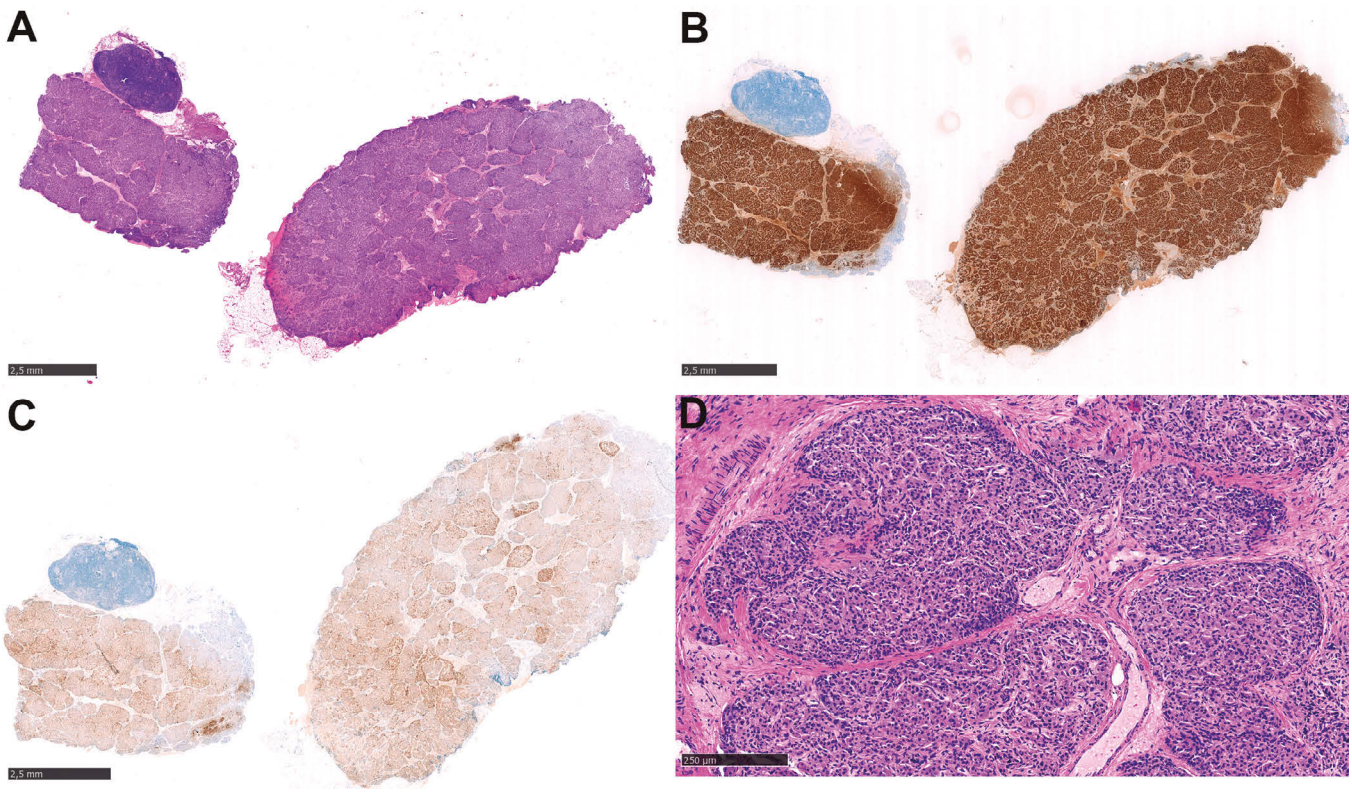

Fig. 2. K_{ATP}-channel focal CHI. **A.** Focal adenomatous hyperplasia (FAH) measuring 12 mm at maximum diameter (H&E). **B.** Strong insulin positivity in beta cells in the FAH (insulin immunostaining). **C.** Delta cells with expression of somatostatin at the periphery of confluent islets of Langerhans in the FAH (somatostatin immunostaining). **D.** High magnification of FAH in focal CHI (H&E). Scale bars: A-C, 2.5 mm; D, 250 µm.

in focal CHI have a large Golgi proinsulin/beta cell area, with strong proinsulin labeling, but relatively few insulin granules and low insulin labeling (Sempoux et al., 1995, 2003), as compared with diffuse CHI.

A significant increase in apoptosis was found in FAH compared with age-matched controls (Kassem et al., 2000). In keeping with these findings, rare patients with suggested K_{ATP}-channel focal CHI not subjected to surgery had spontaneous clinical remission at follow-up (Yorifuji et al., 2011).

Changes in islets outside the focal adenomatous hyperplasia

In many centers performing surgery on patients with CHI, biopsies from different portions of the pancreas are submitted for frozen section analysis to distinguish between focal and diffuse K_{ATP}-channel CHI (Adzick et al., 2004, 2019; Suchi et al., 2004; Barthlen, 2011). For these reasons, it is relevant to be familiar with the histological appearance of the pancreas, not only inside but also outside the FAH. Beta cell nuclear crowding (BCNC) is defined as the number of beta cell nuclei per 1,000 μm^2 of beta cell cytoplasm. A BCNC above 12 was indicative of shrunken insular beta cells outside the FAH in K_{ATP}-channel focal CHI compared with islets from age-matched controls and K_{ATP}-channel diffuse CHI (Sempoux et al., 1998b, 2003). The mean radius of the 50 largest beta cell nuclei was below 3.70 µm outside the FAH in K_{ATP}-channel focal CHI and almost always higher in K_{ATP}-channel diffuse CHI (Sempoux et al., 1998b).

Phenotypic diversity of K_{ATP}-channel focal CHI

Rare variants of K_{ATP}-channel focal CHI include multifocal CHI, which is believed to develop due to two or more separate somatic maternal deletions of the 11p15 region in the same patient (Giurgea al., 2006a; Craigie et al., 2018; Ni et al., 2019; Rosenfeld et al., 2021). Moreover, focal-extensive lesions may reach a size greater than 3 cm (Ismail et al., 2012; Kühnen et al., 2014), or even occupy the entire pancreas (Fig. 3) (Giurgea et al., 2006a; Suchi et al., 2006; Rahier et al., 2011; Ismail et al., 2012; Barthlen et al., 2016). The size of the FAH is believed to relate closely to the time of the second somatic hit in the embryonic development of the pancreas, where early somatic 11p15 maternal deletions will lead to larger focal lesions.

Treatment of focal CHI

Focal CHI can be cured by resection of the lesion. Preoperative ^{18}F-DOPA-PET (PET/CT) imaging (Mohnike et al., 2006; Otonkoski et al., 2006; Laje et al., 2013b; Christiansen et al., 2018) is today imperative to localize focal lesions before surgery. If a focal lesion is not macroscopically identified, intraoperative frozen section analysis may be helpful to localize the focal lesions (Adzick et al., 2004, 2019; Suchi et al., 2004; Barthlen, 2011). In many centers, piecemeal resection with multiple frozen sections is used (Suchi et al., 2004; Barthlen et al., 2010; Barthlen, 2011; Pierro and Nah, 2011; Zobel et al., 2020). At our and other centers, intraoperative ultrasound is frequently used to localize small focal lesions (Adzick et al., 2004, 2019; Bendix et al., 2018; Bjarnesen et al., 2021). Rare patients with focal CHI have been managed conservatively with later spontaneous clinical remission, as suggested by ^{18}F-DOPA PET/CT (Mazor-Aronovitch et al., 2007; Yorifuji et al., 2011). Despite surgical cure of HH in focal CHI, neurodevelopmental impairment is still frequently observed due to late diagnosis and insufficient early treatment.

GCK-CHI

Genetic and clinical findings in GCK-CHI

Glucokinase is an enzyme encoded by the *GCK* gene that acts as a glucose sensor in the GSIS pathway and facilitates the phosphorylation of glucose to glucose-6-phosphate (Campbell and Newgard, 2021). Gain-of-function (GOF) mutations in *GCK* lead to a lowered glucose threshold for GSIS with resultant HH (Glaser et al., 1998; Christesen et al., 2002). GCK-CHI may be inherited in a dominant pattern (Glaser et al., 1998; Christesen et al., 2002; Gloyn et al., 2003; Dullaart et al., 2004; Barbetti et al., 2009; Kassem et al., 2010; Martínez et al., 2017; Ping et al., 2019) or occur *de novo* (Cuesta-Muñoz et al., 2004; Meissner et al., 2009; Sayed et al., 2009; Martínez et al., 2017; Ping et al., 2019). To date, at least 17 GOF position variants of *GCK* causing GCK-CHI have been described (Langer et al., 2021). The prevalence of GCK-CHI is estimated to 2% of all patients with CHI (Christesen et al., 2008b; Snider et al., 2013). The clinical picture of GCK-CHI ranges from neonatal-onset severe HH necessitating subtotal pancreatectomy to apparently asymptomatic childhood with adult-onset hypoglycemic attacks (Glaser et al., 1998; Christesen et al., 2002; Gloyn et al., 2003; Cuesta-Muñoz et al., 2004; Dullaart et al., 2004; Wabitsch et al., 2007; Christesen et al., 2008a; Barbetti et al., 2009; Sayed et al., 2009; Kassem et al., 2010; Beer et al., 2011; Challis et al., 2014; Ajala et al., 2016; Martínez et al., 2017; Jannin et al., 2018; Ping et al., 2019).

Histological findings in GCK-CHI

The histology of GCK-CHI has rarely been described because of the rareness of surgically-treated patients. Reported morphologic changes range from normal pancreas to increased islet size or slightly increased nuclei size of single beta cells (Gloyn et al., 2003; Cuesta-Muñoz et al., 2004; Wabitsch et al., 2007; Kassem et al., 2010). However, even when abnormally large nuclei are present, they tend not to reach the size seen in K_{ATP}-channel diffuse CHI, and their frequency is lower (Cuesta-Muñoz

et al., 2004). In one case, only increased beta cell nuclei size was reported (Sayed et al., 2009).

Morphometric and immunohistochemical studies of GCK-CHI

Abnormally large islets were observed in an operated infant with the *GCK* mutation p.Val91Leu (Kassem et al., 2010). The mean area per islet in the head and tail of the pancreas in this infant was around 7,000 μm^2, compared with five age-matched controls with around 1,000-2,000 μm^2 and diffuse CHI around 750-850 μm^2. There may be some uncertainty about the islet sizes measured in this patient, which of course depend on the methods used and the significance that can be achieved due to the limited number of individuals with GCK-CHI in which similar morphometry has been performed. Moreover, it seems that the islets from patients with diffuse CHI and age-matched controls used by Kassem et al. were smaller compared with previous studies (Liu and Potter, 1962). However, ten percent of the islets of Langerhans in Kassem et al.'s case were larger than 13,000 μm^2, and these large islets contained some beta cells with a large nucleus (Kassem et al., 2010). Abnormally large islets were also reported in a patient with a heterozygous *de novo GCK* mutation p.Tyr214Cys (Cuesta-Muñoz et al., 2004). Normal processing of proinsulin (with an absence of cytoplasmic labeling), increased proinsulin labeling in the Golgi area, and low insulin labeling indicate hypersecretion of

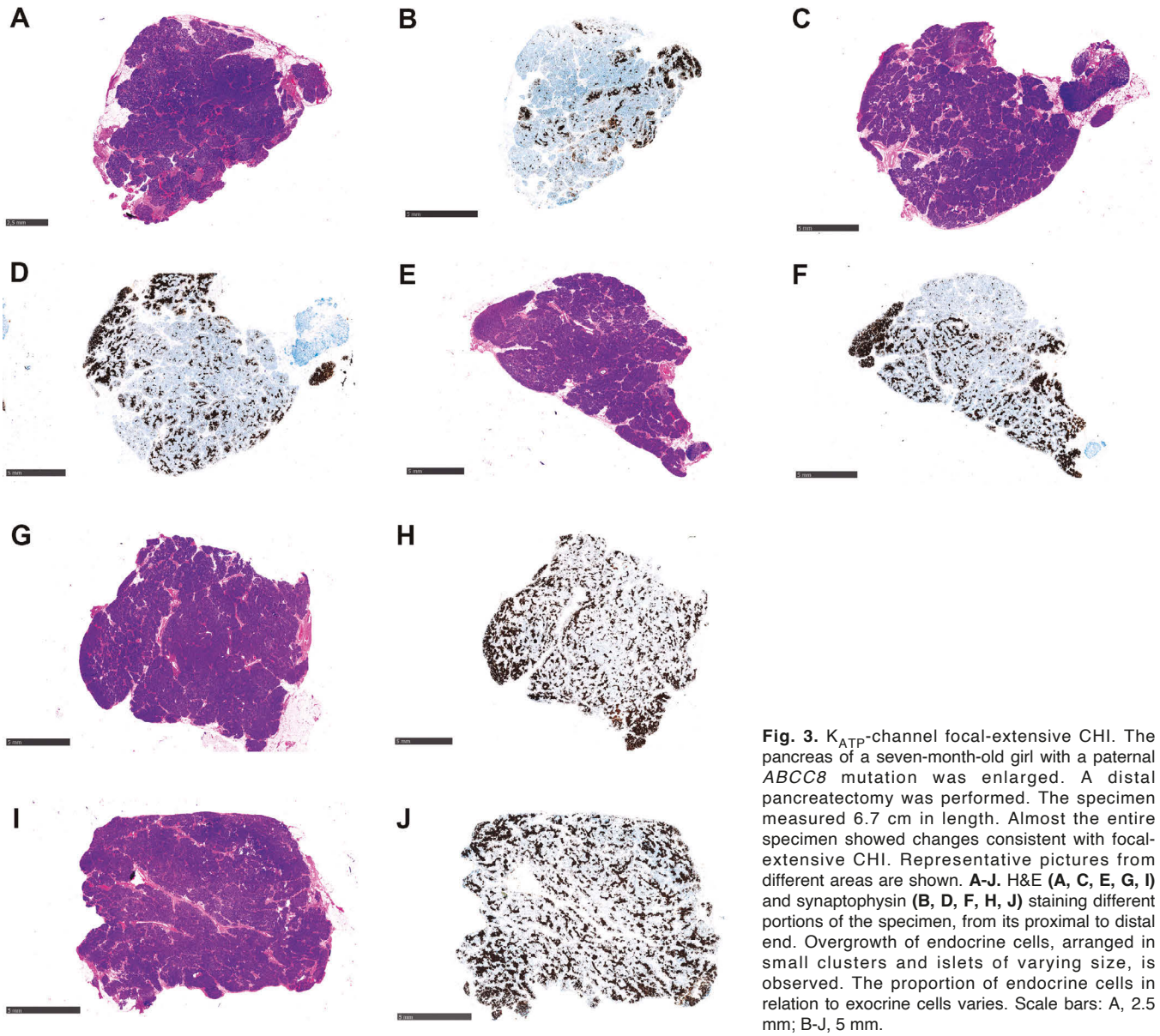

Fig. 3. K_{ATP}-channel focal-extensive CHI. The pancreas of a seven-month-old girl with a paternal *ABCC8* mutation was enlarged. A distal pancreatectomy was performed. The specimen measured 6.7 cm in length. Almost the entire specimen showed changes consistent with focal-extensive CHI. Representative pictures from different areas are shown. **A-J.** H&E **(A, C, E, G, I)** and synaptophysin **(B, D, F, H, J)** staining different portions of the specimen, from its proximal to distal end. Overgrowth of endocrine cells, arranged in small clusters and islets of varying size, is observed. The proportion of endocrine cells in relation to exocrine cells varies. Scale bars: A, 2.5 mm; B-J, 5 mm.

insulin, similar to diffuse and focal CHI (Sempoux et al., 1995, 2003; Klöppel et al., 1999; Cuesta-Muñoz et al., 2004; Rahier et al., 2011). Furthermore, the BCNC was intermediate between age-matched controls, diffuse CHI, and the FAH in K_{ATP}-channel focal CHI (Cuesta-Muñoz et al., 2004). The variations in the histological picture of GCK-CHI seem to reflect variations in glucokinase activity, leading to various degrees of islet size.

Treatment of GCK-CHI

Patients with GCK-CHI do not fully respond to diazoxide, as this drug is not able to correct the lowered threshold for GSIS. Reported GCK-CHI patients had, however, some benefit from diazoxide at low dosages (Meissner et al., 2009; Lord and De León, 2013), yet, this has not been described in detail in the published literature, and there seems to be no effect of this treatment in severe GCK- CHI (Cuesta-Muñoz et al., 2004). Octreotide has been helpful in some cases of GCK-CHI (Wabitsch et al., 2007).

GDH-CHI

Genetic and clinical findings in GDH-CHI

GLUD1 encodes the mitochondrial matrix enzyme glutamate dehydrogenase (GDH), which occurs in the mitochondria of prokaryotes and eukaryotes and is expressed in beta cells (Stanley et al., 1998). GDH-CHI is also known as hyperinsulinism/hyperammonemia syndrome (Stanley et al., 1998). The majority of GDH-CHI cases are due to *de novo* mutations but familial inherited transmitted mutations are also reported (Stanley et al., 1998; De Lonlay et al., 2001; MacMullen et al., 2001; Santer et al., 2001; Stanley, 2004, 2011). GDH is allosterically activated by leucine or ADP and inhibited by guanosine-5'-triphosphate (GTP) and ATP. In GDH-CHI, a GOF mutation in *GLUD1* desensitizes GDH to allosteric inhibition by GTP, while allosteric activation by leucine is uninhibited (Stanley et al., 1998).

GDH-CHI typically results in milder HH compared with K_{ATP}-channel CHI and is usually not detected until patients are at least a few months old (De Lonlay et al., 2001; Stanley, 2004; Kapoor et al., 2009), although cases may already present at day 1 (Yorifuji et al., 1999; Stanley et al., 2000; MacMullen et al., 2001).

GDH-CHI is characterized by normal birth weight and protein-meal-induced postprandial hypoglycemia with persistent asymptomatic hyperammonemia (Stanley et al., 2000; Hsu et al., 2001; Stanley, 2004; Kapoor et al., 2009; Palladino and Stanley, 2010). However, some patients show completely normal ammonia levels, probably due to mosaicism of the genetic changes (Kapoor et al., 2009). Barrosse-Antle et al. reported a severe case with homozygous activating *GLUD1* mutations in exon 6 and 7, presenting with hypoglycemia, hyperammonemia, and seizures immediately after birth (Barrosse-Antle et al., 2017).

Histological findings in GDH-CHI

Rahier et al. analyzed two surgical GDH-CHI cases (Rahier et al., 2011). The specimens were macroscopically unremarkable. Microscopically, a few beta cell nuclei showed a moderate increase in size but the cytoplasm remained unchanged. With IHC, insulin staining was not lowered as in diffuse CHI and proinsulin expression was high. SUR1 expression was normal, compatible with a normally functioning K_{ATP}-channel. In a specimen from another surgically treated GDH-CHI patient, hypertrophic islet cells were arranged in ribbon-like patterns (De Lonlay et al., 2001). These morphological changes seem to reflect a clinically milder form of HH than K_{ATP}-channel diffuse CHI (Stanley, 2004).

Treatment of GDH-CHI

Management of GDH-CHI includes diazoxide and a diet restricted in protein, especially leucine (Kapoor et al., 2009; Stanley, 2011; Roy et al., 2019). Surgery is very rarely performed, as GDH-CHI usually responds to diet and diazoxide (Stanley et al., 2000; MacMullen et al., 2001).

CHI in Beckwith-Wiedemann syndrome (BWS-CHI)

Genetic and clinical findings in BWS-CHI

BWS is the most common pediatric overgrowth syndrome with an estimated prevalence of 1:10,000-13,700 (Thorburn et al., 1970; Mussa et al., 2013). BWS is frequently diagnosed in the neonatal period or early childhood and is typically characterized by macroglossia, macrosomia, abdominal wall defects, asymmetric overgrowth, and increased risk of embryonal tumor development (DeBaun and Tucker, 1998; Weksberg et al., 2010; Kalish et al., 2016; Maas et al., 2016; Brioude et al., 2018).

As overgrowth affects a variable part of cells during embryogenesis, a broad BWS spectrum of clinical features with varying severity is seen (Kalish et al., 2016; Brioude et al., 2018; Wang et al., 2019).

HH is seen in 50% of patients with BWS and is usually mild and transient with resolution within a few days (Mussa et al., 2016a). In 5% of cases, however, persistent hypoglycemia is observed (Elliott et al., 1994; DeBaun et al., 2000). The severity of HH in BWS is thought to be related to the variable percentage of mosaic changes within the pancreas (Kalish et al., 2016).

BWS is caused by genetic and epigenetic changes in the imprinting centers IC1 and IC2 on chromosome 11p15.5-11p15.4, containing the genes *CDKN1C*, *H19*, *IGF2*, and *KCNQ1* (Kalish et al., 2016; Mussa et al., 2016b; Brioude et al., 2018). An (epi-) genetic defect is seen in 80% of BWS patients (Choufani et al., 2010; Eggermann et al., 2014; Brioude et al., 2018). The majority of patients with BWS are sporadic and 15%

have a familial predisposition (Viljoen and Ramesar, 1992; Choufani et al., 2010; Eggermann et al., 2014; Brioude et al., 2018). In sporadic cases, about 50% have loss-of-methylation of IC2 in the maternal allele, 20% have pUDP of chromosome 11p15, 5% have gain-of-methylation of IC1 in the maternal allele, and 5% have a mutation in *CDKN1C* (Choufani et al., 2010; Eggermann et al., 2014; Brioude et al., 2018). A maternal *CDKN1C* mutation can be detected in 40% of familial cases (Choufani et al., 2010; Eggermann et al., 2014; Brioude et al., 2018). The 11p15.5-11p15.4 changes commonly lead to mosaic overgrowth. Mosaic pUPD is occasionally seen for the entire chromosome 11, which does not seem to affect the clinical features, compared to cases where only a small part of this chromosome is affected (Dutly et al., 1998; Cooper et al., 2007). In rare cases, the genome-wide pUPD may lead to additional syndromic manifestations, including BWS-CHI (Giurgea et al., 2006b; Wilson et al., 2008; Gogiel et al., 2013; Kalish et al., 2013; Christesen et al., 2020).

Persistent HH in BWS is almost exclusively due to pUPD of chromosome 11p15 (Kalish et al., 2016). Moreover, paternally inherited pathogenic K_{ATP}-channel mutations may occur in addition to overexpression of *IGF2* and reduced expression of *H19* and *CDKN1C* (Kalish et al., 2016). Hence, mosaic pUPD can uncover a recessive pathogenic K_{ATP}-channel mutation resulting in HH, as also suggested by other studies (Calton et al., 2013; Kocaay et al., 2016).

Histological findings in BWS-CHI

In surgical pancreas specimens from patients with BWS-CHI, a distinct histological picture is characterized by overgrowth with an increase in the volume of endocrine cells (Fig. 4) (Hussain et al., 2005; Laje et al., 2013a; Christesen et al., 2020). The degree of morphological mosaicism in the resected pancreatic tissue varies from a focal or segmental lesion, sometimes several, to the inclusion of the entire pancreas (Kalish et al., 2016).

In contrast to K_{ATP}-channel focal CHI, the endocrine cells are arranged in small clusters, often enlarged islets and groups, but usually not confluent islets (Fig. 4D-F). Between the endocrine islets and cell clusters, acinar cells and small ducts are observed (Christesen et al., 2020).

Morphometric and immunohistochemical studies of BWS-CHI

In a small study, the density of nuclei in the endocrine lesion was around 4,000 nuclei per 0.4 mm^2 in a BWS-CHI patient, compared with around 2,500 nuclei per 0.4 mm^2 in five randomly selected specimens with focal CHI (Christesen et al., 2020). Strong proinsulin expression was reported in BWS-CHI, but insulin immunostaining was weak (Hussain et al., 2005). Expression of p57 was seen in approximately 5% of the endocrine cells (Christesen et al., 2020), in contrast with K_{ATP}-channel focal CHI, where p57 expression is absent (Kassem et al., 2001; Sempoux et al., 2003). Larger studies using morphometry in BWS-CHI are, to our knowledge, currently lacking.

Treatment of BWS-CHI

For patients with BWS-CHI who are unresponsive to medical treatment, pancreatic resection is required. Preoperative ^{18}F-DOPA-PET (PET/CT) can be useful to determine the size of the overgrowth area and to exclude focal CHI (Laje et al., 2013a). Even severe and prolonged BWS-CHI can improve over time, which may call for prolonged medical treatment (Laje et al., 2013a).

Morphological mosaicism of pancreatic islets

Genetic findings in morphological mosaicism of pancreatic islets

Rare non-syndromal CHI patients subjected to pancreatic surgery have shown a mosaic histological picture without overgrowth, with normal SUR1 expression in the islets, and absence of germline mutations in known CHI genes (Sempoux et al., 2011). In five of these patients, hexokinase 1 (HK-1), was inappropriately expressed in hyper-functional type 1 islets. The five patients were preoperative responsive, or at least transient sensitive, to diazoxide (Henquin et al., 2013). Using Sanger sequencing, a heterozygous somatic *GCK* variant, p.IIe211Phe, was later reported in one of the patients from Sempoux's cohort (Henquin et al., 2013).

Although not always fully described, somatic mosaicism on the (epi-)genetic level in leukocyte DNA or pancreatic tissue is probably closely correlated with the morphological mosaic histological picture, with or without overgrowth. The emerging genetic heterogeneity of mosaic, non-syndromal CHI will probably in future lead to a more detailed phenotypic characteriza-tion, according to the affected genes and the degree of mosaicism in the pancreatic tissue.

Clinical findings in morphological mosaicism of pancreatic islets

Compared with focal and diffuse CHI, patients with non-syndromal mosaicism of pancreatic islets had a lower birth weight and later onset of HH, median (range) 165 (1-270) days (Sempoux et al., 2011).

Histological findings in morphological mosaicism of pancreatic islets

In the important study of Sempoux et al. (Sempoux et al., 2011), CHI without the histological features of focal CHI, diffuse CHI, GCK-CHI, GDH-CHI, or BWS-CHI was described in 16 patients with unknown genetics. The

pancreas appeared macroscopically normal. Histologically, the coexistence of two different islet types was observed (Sempoux et al., 2011). Type 1 islets were hyperplastic, being around two-fold larger than type 2 islets, and confined to one or several adjacent lobules. Type 2 islets were small, shrunken, and distributed throughout the entire pancreas (Sempoux et al., 2011). This histological pattern may well be caused by as yet unidentified somatic, mosaic gene mutations restricted to the endocrine cells in type 1 islets, as later proven for a fraction of the patients. It is possible that the three cases published by Han and coworkers also represent morphological mosaicism of islets (Han et al., 2017).

Morphometric and immunohistochemical findings in morphological mosaicism of pancreatic islets

Morphometric analyses showed that type 1 islets had a mean area of around 11,400 µm^2 (Sempoux et al., 2011). Type 1 islets also contained numerous beta cells with abundant cytoplasm and sometimes large nuclei, however, rarely as large as in diffuse CHI. The radius of

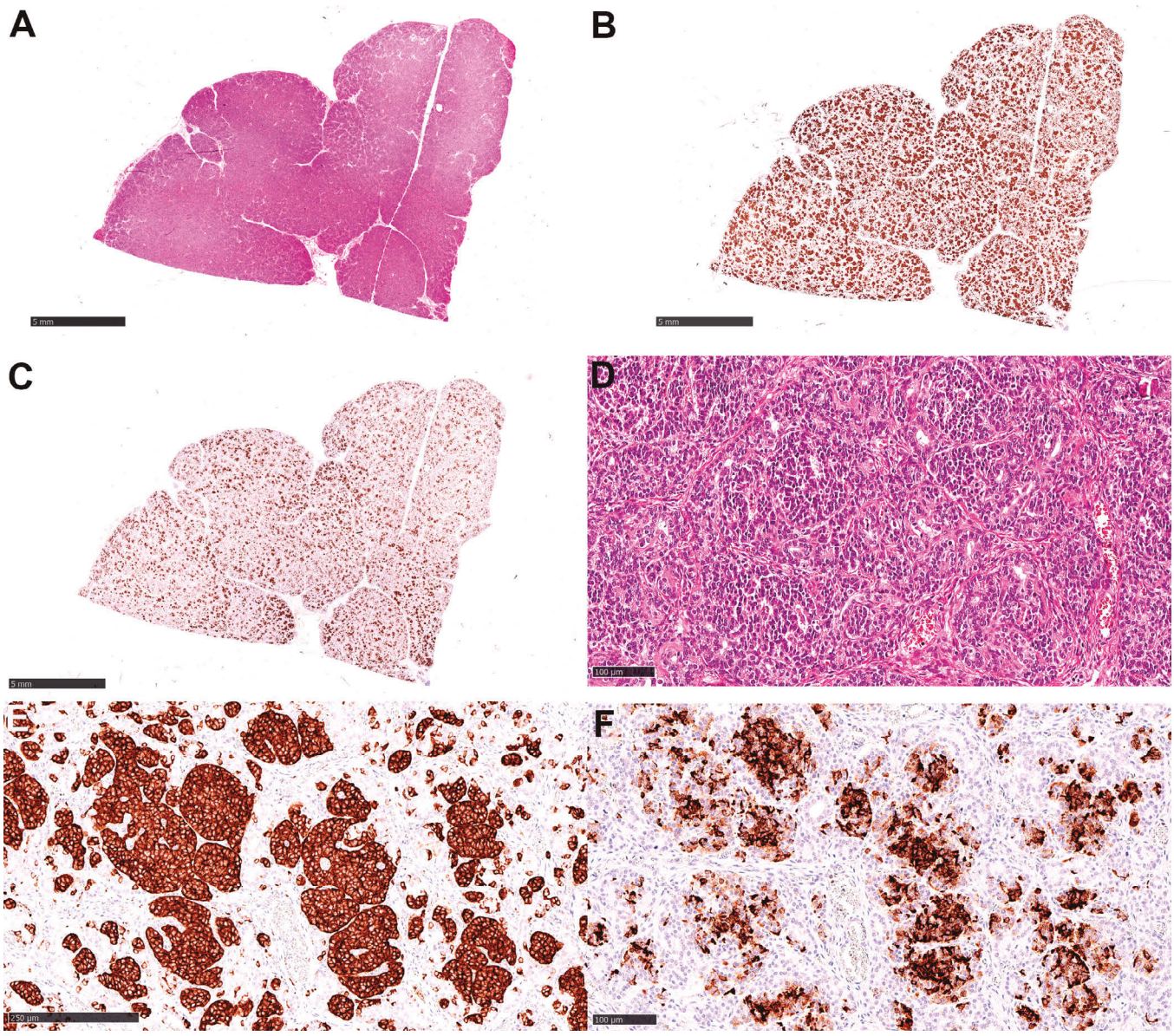

Fig. 4. CHI in Beckwith-Wiedemann syndrome (BWS-CHI). **A-C.** H&E **(A)**, synaptophysin **(B)**, and insulin **(C)** staining of a portion of the surgically resected pancreas. Overgrowth with an increase in the volume of endocrine cells in this area is shown. **D-F.** H&E **(D)**, synaptophysin **(E)**, and insulin **(F)** staining at higher magnification. The endocrine cells are arranged in small clusters, often enlarged islets, and in groups. between the endocrine islets and cell clusters, acinar cells and small ducts are observed. Scale bars: A-C, 5mm; D, F, 100 µm; E, 250 µm.

beta cell nuclei was around 5-6 µm in type 1 compared with around 4 µm in type 2 islets. In accordance with this, the BCNC was higher in type 2 vs. type 1 islets (around 14 vs. 9). Also, insulin expression was higher in type 1 than in type 2 islets (Sempoux et al., 2011). p57 expression was present in both types of islets. The area of type 2 islets is not given in the article, but it was stated that type 1 islets were 2.06 fold larger than type 2 islets. The mean area in type 1 islets was 11,400 μm^2, roughly corresponding to a mean diameter of around 0.12 mm. This would mean that type 2 islets, in the study by Sempoux and coworkers, may have had a mean diameter of roughly 0.08 mm, corresponding to a mean area of 5.540 μm^2 (Sempoux et al., 2011).

Differential diagnosis of morphological mosaicism of pancreatic islets

Segmental, or localized Islet Nuclear Enlargement (LINE) has been introduced as a morphological type of CHI (Adzick et al., 2019). Recently, a series of 12 cases of patients with pancreatic histology consistent with LINE were published (Boodhansingh et al., 2022b). Morpho-logically, islet cell nucleomegaly was identified in one or two contiguous regions of the pancreas. Genetically, low-level mosaic mutations were identified in the pancreas of six cases (three in *ABCC8*, three in *GCK*), out of eight cases where this analysis was done (Boodhansingh et al., 2022b). Hence, it seems that LINE, is characterized by a morphology different from the morphological mosaicism of islets described above, based on data available so far.

Other less clear mosaic genotype-histotype correlations have been described, including combinations of 11pUPD and a germline or somatic mosaic *ABCC8* variant in affected parts of the pancreas (Hussain et al., 2008) and germline and somatic mosaic *GLUD1* mutations, but with reportedly diffuse histology without further details (Boodhansingh et al., 2022a).

In conclusion, mosaic mutations in several known CHI genes lead to mosaic histotypes and often less severe clinical hyperinsulinism compared to non-mosaic mutations in the same genes. A more detailed description of the potential different mosaic histotypes is warrented.

Treatment of morphological mosaicism of pancreatic islets

All patients with morphological mosaicism were (at least partially) responsive to diazoxide treatment, however, with decreasing sensitivity over time, necessitating surgery. After surgical intervention, medical treatment was usually not necessary (Sempoux et al., 2011).

Other forms of hyperinsulinemic hypoglycemia

Other rare syndromic or non-syndromic genotypes with CHI lack histological descriptions, as they usually can be managed conservatively without surgery. This includes CHI in association witih mutations in *ADK* (ADK deficiency); *ALG3* (Congenital Disorder of Glycosylation (CDG) type 1D); *ARID12* (Coffin-Siris syndrome); *CACNA1C* (Timothy syndrome); *CACNA1D* (PASNA syndrome); *CCND2* (Mega-encephaly-polymicrogyria syndrome); *CHD7* (Charge syndrome); *CREBBP* and *EP300* (Rubinstein-Taybi syndrome); *DIS3L2* (Perlman syndrome); *EIF2S3* (MEMHO syndrome); *FAH* (Tyrosinemia type 1); *FOXA2* (Pituitary hypoplasia-CHI syndrome); *GPC3* (Simpson-Golabi-Behmel syndrome); *HADH*, *HNF1A*, *HNF4A*, and *HRAS* (Costello syndrome); *INSR* and *JAG1* (Alagille syndrome type 1); *KCNQ1*, *KDM6A*, and *KMT2D* (Kabuki syndrome); *MAGEL2* (Schaaf-Yang syndrome); *MPI* (CDG type 1B); *NFIX* (Malan syndrome); NSD1 (SOTOS syndrome); *PGM1* (CDG type 1T); *PMM2* (CDG type 1A, polycystic kidney disease); *PHOX2B* (congenital central hypoventilation); *SLC16A1* (MCT, exercise-induced hyperinsulinism); *SCL25A36* and *TRMT10A* (MMSGM1 syndrome); *UCMA* (Poland syndrome); *UCP2* and *YARS1* (YARS syndrome) (Rosenfeld et al., 2019; Kostopoulou et al., 2021; Hewat et al., 2022; Shahroor et al., 2022). Moreover, a number of contiguous gene deletions have been related to CHI.

Of special note, dominant inactivating mutations in the transcription factors *HNF4A* and *HNF1A* result in Maturity-onset diabetes of the young (MODY) type 1 and type 3, respectively, however, in some patients also macrosomia at birth and diazoxide-responsive HH with spontaneous clinical remission (Pearson et al., 2007; Flanagan et al., 2010; Dusatkova et al., 2011; Stanescu et al., 2012; McGlacken-Byrne et al., 2014; Tung et al., 2018; McGlacken-Byrne et al., 2022). Patients with mutations in a number of other genes may also undergo spontaneous transition to diabetes without pancreatic surgery. Inhibiting *INSR* mutations lead to insulin resistance, usually presenting with permanent neonatal diabetes, but milder cases may have late disease onset with HH as the presenting feature due to a prolonged insulin half-life in the circulating blood (Rosenfeld et al., 2019; Hewat et al., 2022).

Insulinoma

An insulinoma is a functioning NET with unregulated hyperproduction of insulin and resultant HH (Guettier and Gorden, 2010). The incidence of insulinoma is estimated at 1:250.000 in the Mayo Clinic, USA (Service et al., 1991).

Genetic findings in insulinoma

Most insulinomas arise sporadically (Shin et al., 2010). In adults, 4-8% are associated with MEN1 (Service et al., 1991; Anlauf et al., 2009; Placzkowski et al., 2009; Crippa et al., 2012; Kurakawa et al., 2021; Svensson et al., 2022) due to autosomal dominantly inherited mutations in the tumor suppressor gene *MEN1* (Larsson et al., 1988; Byström et al., 1990; Chandrasekharappa et al., 1997). While insulinoma is

rarely a part of MEN1 in adults, MEN1-associated insulinomas are commonly seen in children with this syndrome, accounting for 38-42% of all cases (Bhatti et al., 2016; Melikyan et al., 2023). In children, insulinomas may often be the first presentation of MEN1 (van Beek et al., 2020), in contrast to parathyroid adenomas as the most frequent first presentation of MEN1 in adults (Thakker et al., 2012). The *MEN1* gene is located on chromosome 11q13, and the presumed somatic second hit in the insulinoma may be caused not only by a second *MEN1* mutation, but also by deletion of the entire maternal chromosome 11 including the tumor suppressor region 11p15 (Bhatti et al., 2016). The authors found evidence of maternal loss of heterozygosity for 11p15 in both MEN1-associated and sporadic insulinomas. Moreover, aneuploidy of other chromosomes was reported (Bhatti et al., 2016).

MEN1 mutations are uncommon in sporadic insulinomas (Cupisti et al., 2000; Jonkers et al., 2005). In three next-generation sequencing studies, somatic *MEN1* mutations were revealed in appro-ximately 2.4% of all insulinomas (Cao et al., 2013; Wang et al., 2017; Hong et al., 2020). Somatic mutations in other genes have also been reported in insulinomas, including *ARHGAP35*, *ATR*, *FLNC*, *H3F3A*, *KDM6A*, *LMO2*, *MLL3*, and *YY1* (Cao et al., 2013; Wang et al., 2017; Hong et al., 2020). In a recent whole-genome sequencing study, the most frequent somatic mutations were found in *YY1* (25%), *DOCK4* (4%), *EVA1X* (2%), and *FRG1* (2%) (Hong et al., 2020). In pancreatic non-functioning NETs, on the other hand, others found frequent somatic mutations in *MEN1* (42%), followed by *DAXX* (21%), *ATRX* (13%), *PTEN* (9%), and *SETD2* (5%). The same mutations are rarely involved in insulinomas (Hong et al., 2020). More studies on a larger number of insulinomas are needed on the genetic background for the development of insulinomas with and without hereditary or somatic *MEN1* mutations.

Clinical findings in insulinoma

Insulinomas in children are rare (Boley et al., 1960; Mann et al., 1969; Service et al., 1991; Padidela et al., 2014; Bhatti et al., 2016; Melikyan et al., 2023). In a 60-year-study including 224 patients, only 6% of the insulinomas occurred in adolescents or children under the age of 19 (Service et al., 1991), and the youngest children were 3-4 years old (Boley et al., 1960; Mann et al., 1969; Service et al., 1991; Padidela et al., 2014; Bhatti et al., 2016). Hence, it is unlikely that an insulinoma is the cause of HH before the age of 2-3 years.

In a large series of insulinoma patients, the median age at the time of surgery was 47 (range 8-82) years, with females constituting 59%. Almost 87% had a single insulinoma, 7.1% had multiple insulinomas, and 5.8% had aggressive insulinomas (Service et al., 1991). Sporadic insulinomas are typically solitary, but insulinomas associated with MEN1 are frequently multicentric (Demeure et al., 1991; van Beek et al., 2020). Insulinoma with and without *MEN1* mutations can be malignant but behaves mostly as non-malignant (Placzkowski et al., 2009; Bartsch et al., 2013; Andreassen et al., 2019). The Ki67 index predicts the probability of metastasis, but even insulinomas with a low Ki67 index can metastasize and occasionally benign insulinomas show a high Ki67 index (Alkatout et al., 2015; Andreassen et al., 2019; Sada et al., 2021). Malignant insulinomas are not, or very rarely, seen in children (Service et al., 1991; Jaksic et al., 1992; Janem et al., 2010; Bhatti et al., 2016).

The clinical diagnosis of insulinomas is first based on Whipple's triad with signs and symptoms of hypoglycemia, low blood glucose, and resolution of symptoms after rising blood glucose (Whipple, 1938). Insulinomas can be difficult to diagnose as symptoms may be non-specific and present for a long period before diagnosis (Service, 1995; Boukhman et al., 1998; Grant, 1998). A 48h, or 72h, fasting test is the gold diagnostic test for the detection of HH in adults (Service, 1995; Hirshberg et al., 2000; de Herder et al., 2006; Vezzosi et al., 2007; Placzkowski et al., 2009; Toaiari et al., 2013). In the case of a negative fasting test, an oral glucose tolerance test may provoke rebound hypoglycemia due to insulin excess (Falconi et al., 2016). The presence of an insulinoma is associated with high levels of circulating proinsulin, consistent with histopathology findings suggesting insufficient insulin processing, rather than high insulin secretion (Roth et al., 1992; Azzoni et al., 1998; Wiesli et al., 2004; Guettier et al., 2013). A higher proinsulin/insulin ratio is often seen in malignant insulinomas compared with benign insulinomas (Yu et al., 2017). Imaging to detect and localize the insulinoma may be difficult despite the many available imaging technique modalities, including ultrasound, CT, MRI, and various PET scan tracers, as discussed in a recent review (Prosperi et al., 2022).

Histological findings in insulinoma

Insulinomas are often well-delimited endocrine tumors (Fig. 5) (Sempoux et al., 2003; Padidela et al., 2014; Bhatti et al., 2016). The tumors are distributed equally in the different regions of the pancreas (Shin et al., 2010). Insulinomas typically range from 5 to 24 mm (Klöppel and Heitz, 1988; Solcia et al., 1997; Sempoux et al., 2003; Bhatti et al., 2016) and insulinomas exceeding 3 cm in diameter increase the risk of malignancy (Solcia et al., 1997; Câmara-de-Souza et al., 2018; Andreassen et al., 2019; Sada et al., 2021). Their cut surface is typically grey-white to red-pink-brown (Solcia et al., 1997; Komminoth et al., 1999; Sempoux et al., 2003). The consistency is soft compared with the normal surrounding yellowish pancreatic parenchyma except in cases with fibrous stroma and/or large amounts of amyloid (Solcia et al., 1997; Komminoth et al., 1999; Sempoux et al., 2003; Bhatti et al., 2016). Different growth patterns can be observed, for example, nets or cords separated by vascularized fibrous stroma (Sempoux et al., 2003; Padidela et al., 2014; Bhatti et al.,

2016). The tumor cells are relatively uniform, cylindrical, or cuboidal-shaped with moderately abundant acidophilic cytoplasm (Sempoux et al., 2003).

Insulinomas express mainly insulin (Fig. 5B), but expression of glucagon, somatostatin, and even pancreatic polypeptide is also observed in about half of cases (Liu et al., 1985; Solcia et al., 1997; Komminoth et al., 1999; Sempoux et al., 2003; Bhatti et al., 2016). In addition, general neuroendocrine markers, such as chromogranin A and synaptophysin (Fig. 5C), are strongly expressed. As with other neuroendocrine neoplasms, insulinomas are graded according to their Ki67 and mitotic index: NET grade 1 shows a Ki67-index of <3% (and <2 mitoses per 2 mm^2); grade 2 between 3% and 20% (Fig. 5C) (and 2-20 mitoses per 2 mm^2); grade 3 above 20% (and >20 mitoses per 2 mm^2). Neuroendocrine carcinomas show necrosis and an aggressive infiltration growth, in addition to a Ki67-index >20% (often >90%), and >20 mitoses per 2 mm^2 (Lloyd, 2017). Most insulinomas are low-grade tumors

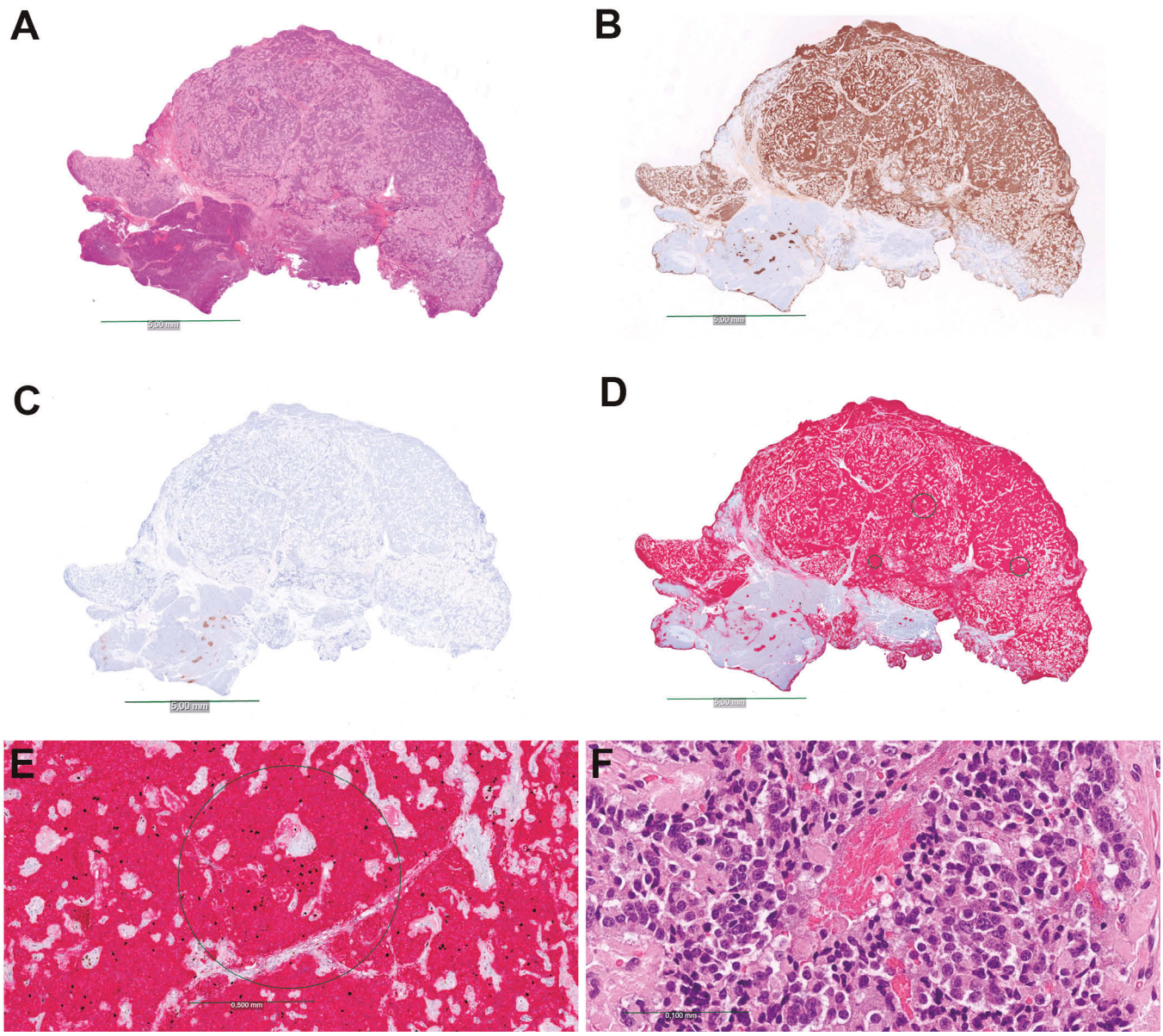

Fig. 5. Insulinoma that resulted in hyperinsulinemic hypoglycemia. **A.** A well-circumscribed tumor consisting of confluent trabeculae supported by a hyalinized fibrotic stroma (H&E). **B.** Strong expression of insulin in the tumor cells (insulin immunostaining). **C.** Lack of glucagon expression in the tumor cells (glucagon immunostaining). **D.** A Ki67 proliferation index in hot spots of 7%, corresponding to tumor grade 2 (dual-IHC of synaptophysin (red) and Ki67 (brown)). **E.** Higher magnification of **(D)**. **F.** Nuclei of insulinoma cells show salt and pepper chromatin (H&E). Scale bars: A-D, F, 5.0 mm; B, 0.1 mm.

(Bhatti et al., 2016).

Treatment of insulinoma

Surgery is the optimal treatment for insulinomas (de Carbonnières et al., 2021). Diazoxide is the primary choice for treating the symptoms of non-resectable insulinomas and is effective in 50-60% of patients (Mathur et al., 2009; Öberg, 2018; Niitsu et al., 2019). In diazoxide non-responders with non-resectable malignant insulinomas, somatostatin agonists can be used because of their antiproliferative effect (Matej et al., 2016; Brown et al., 2018).

Insulinomatosis

Insulinomatosis is a rare cause of HH in adults and is characterized by multiple small and large insulin-producing tumors (Anlauf et al., 2009). Insulinomatosis is a very rare neoplastic condition; in a large series of patients with insulinomas, insulinomatosis accounted for approximately 5% (Anlauf et al., 2009). To date, at least 18 cases of sporadic insulinomatosis (Anlauf et al., 2009; Snaith et al., 2020; Anoshkin et al., 2021; Mintziras et al., 2021; Tartaglia et al., 2022) and three cases with familial insulinomatosis (Tragl and Mayr, 1977; Iacovazzo et al., 2018; Fottner et al., 2022) have been reported.

Genetic and clinical findings in insulinomatosis

Germline mutations in the *MAFA* gene have been identified in familial insulinomatosis in three unrelated families with an autosomal dominant pattern (Iacovazzo et al., 2018; Fottner et al., 2022). Other family members with the same *MAFA* mutation develop impaired glucose tolerance or diabetes. In addition, congenital glaucoma or cataract may be present (Iacovazzo et al., 2018; Fottner et al., 2022). In one case of sporadic insulinomatosis, a germline *MAFA* in-frame deletion, p.His207del, has been reported (Mintziras et al., 2021).

MAFA encodes the transcription factor MAFA, which regulates the beta cell expression of insulin and several genes involved in GSIS (Liang et al., 2022). Moreover, the two reported familial missense mutations, p.Ser64Phe and p.Thr47Arg, impair MAFA phosphorylation leading to decreased proteasome-mediated degradation and, hence, increased MAFA protein stability as a potential, at least partial, mechanism for the oncogenic capacity of these *MAFA* mutations (Iacovazzo et al., 2018; Fottner et al., 2022). The mechanisms for the development of both diabetes and insulinomatosis in *MAFA* patients are not fully understood.

Histological findings in insulinomatosis

Insulinomatosis is histologically characterized by multiple macro-tumors (>5 mm) and micro-adenomas (<5 mm) that express insulin and arise synchronously and metachronously in all regions of the pancreas; metastases are rarely seen (Anlauf et al., 2009).

Insulinomatosis is distinguished histologically by insulin-expressing mono-hormonal endocrine cell clusters. The tumors only stain for insulin (Anlauf et al., 2009), whereas micro-adenomas in MEN1 patients often express glucagon and pancreatic polypeptide (Anlauf et al., 2006). Other micro-adenomas express glucagon (glucagon-cell adenomatosis), or no hormones, as seen in von Hipple-Lindau syndrome (Périgny et al., 2009; Zhou et al., 2009; Miller et al., 2015).

Treatment of insulinomatosis

Treatment of insulinomatosis is complicated due to the multicentric nature of the disease. In a large study, 43% of patients had persistent or recurrent disease following surgical treatment, sometimes necessitating additional surgery (Anlauf et al., 2009). Medical therapy is often not successful, but one patient with sporadic insulinomatosis showed complete remission after treatment with octreotide long-acting release (Tartaglia et al., 2022).

Adult-onset non-insulinoma persistent hyperinsulinemic hypoglycemia syndrome

Terminology

Adult-onset NI-PHHS has alternatively been abbreviated NIPH (Vanderveen et al., 2010; Anderson et al., 2016), NI-PHH (Christesen et al., 2008b), NIPHS (Thompson et al., 2000; Anlauf et al., 2005; Won et al., 2006; Sahloul et al., 2007; Yamada et al., 2020), or non-insulinoma pancreatogenous hypoglycemic syndrome (PHH) (Klöppel et al., 2008). Adult nesidioblastosis is an alternative historical, yet incorrect, histological term in today's view.

Genetic and clinical findings in NI-PHHS

NI-PHHS is an entity that mainly affects adults, with rare cases seen in adolescence (age range from 12-82 years) (Harness et al., 1981; Service et al., 1999; van der Wal et al., 2000; Witteles et al., 2001; Kaczirek et al., 2003; Anlauf et al., 2005; Won et al., 2006; Raffel et al., 2007; Yamada et al., 2020). Most patients with NI-PHHS have an unknown genetic cause. However, *GCK* mutations have been found in a few adults with clinical features of NI-PHHS, suggesting a genetic cause in at least some patients (Glaser et al., 1998; Christesen et al., 2008a). Yet, histology was not available in these studies (Glaser et al., 1998; Christesen et al., 2008a). Other rare adult patients presented with exercise-induced HH due to activating mutations in the *SLC16A1* promotor, none of these patients were subjected to pancreatic surgery (Otonkoski et al., 2003, 2007). Insulinoma is the most important clinical differential diagnosis. NI-PHHS has, in a large series, been identified in 3-8.5% of clinically

diagnosed insulinomas (Anlauf et al., 2005; Raffel et al., 2007; Yamada et al., 2020). Another and more frequent cause of HH in adults is postprandial HH after gastric bypass surgery, a secondary condition which should be discerned from NI-PHHS as a primary disease (Thompson et al., 2000; Raffel et al., 2007; Yamada et al., 2020).

The clinical symptoms of NI-PHHS are usually observed during fasting, exercise, or stress, and are related to autonomic and severe neuroglycopenic hypoglycemia, leading to confusion, visual disturbances, dizziness, abnormal behavior, loss of consciousness, sweating, palpitations, and tremor (Goossens et al., 1991; Service et al., 1999; van der Wal et al., 2000; Witteles et al., 2001; Kaczirek et al., 2003; Otonkoski et al., 2007). A 72-h fast is a standard test in the diagnostic process for NI-PHHS (Service, 1995), but is unspecific in distinguishing NI-PHHS from insulinoma (Service, 1999; Kaczirek et al., 2003; Starke et al., 2006; Won et al., 2006).

Histological findings in NI-PHHS

In surgical pancreas specimens from NI-PHHS

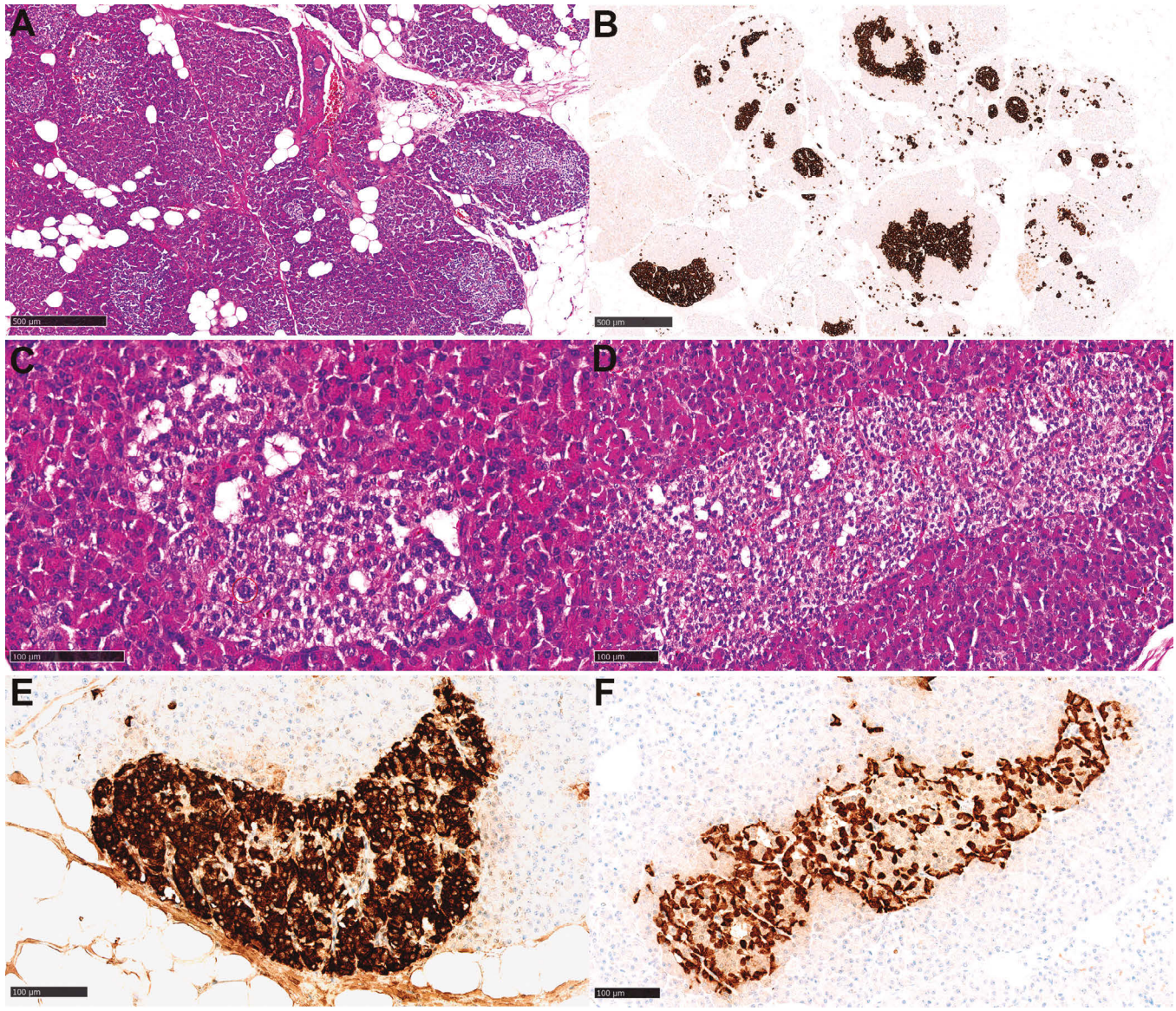

Fig. 6. Adult-onset non-insulinoma hyperinsulinemic hypoglycemia syndrome (NI-PHHS). **A.** Number and size of islets of Langerhans are slightly increased compared with normal adults (H&E). **B.** Synaptophysin immunostaining emphasizes several enlarged pancreatic islets. **C.** A pancreatic islet showing slight variation in the size of beta cell nuclei, which can also be seen in healthy adult pancreas. **D-F.** Enlarged islet of Langerhans with a length of around 800 µm. **D.** H&E. **E.** Normal amount of insulin-positive beta cells (insulin immunostaining). **F.** Normal amount of glucagon-positive alpha cells (glucagon immunostaining). Scale bars: A, B, 500µm; C-F, 100µm.

patients, the macroscopic appearance is usually normal (Anlauf et al., 2005). In around a third, the histological changes in the endocrine pancreas were minimal and difficult to distinguish from normal pancreatic tissue (Klöppel et al., 2008). A feature of the islets in the remaining cases was a somewhat lobulated composition, probably resulting from irregularly sized beta cells that form small groups within the islets (Anlauf et al., 2005). In a proportion of cases, however, the number and size of pancreatic islets are slightly increased (Fig. 6). Major histopathologic criteria for the histological diagnosis of NI-PHHS are 1) exclusion of an insulinoma, 2) multiple beta cells with enlarged and hyperchromatic nuclei and abundant cytoplasm, 3) islets with a normal composition of endocrine cell types, and 4) no increased proliferative activity of endocrine cells (Anlauf et al., 2005). Minor histopathologic criteria are 1) irregular shape and occasional enlargement of islets (Fig. 6D), 2) increased number of islets (Fig. 6A,B), 3) lobulated islet structure, and 4) macronuclei in beta cells (Fig. 6C) (Anlauf et al., 2005). Unfortunately, these criteria are relatively unspecific.

Morphometric and immunohistochemical studies of NI-PHHS

Single islets in NI-PHHS are enlarged, with a diameter of 300 μm or more (Fig. 6D-F) (Harness et al., 1981; Volk and Wellmann, 1985; van der Wal et al., 2000; Kaczirek et al., 2003; Anlauf et al., 2005). As a consequence, an increased total beta cell volume can be measured (van der Wal et al., 2000; Anlauf et al., 2005). Beta cells show enlarged nuclei and abundant clear cytoplasm. Macronuclei were observed more often than in controls (van der Wal et al., 2000; Witteles et al., 2001; Anlauf et al., 2005). Overexpression of islet neogenesis-associated protein was reported in a few cases (Won et al., 2006). More research with the identification of (epi-)genetic, germline, or somatic mutations, or altered regulation of insulin production or secretion, is needed to further describe the pathophysiology and related histological features of NI-PHHS. Most probably, subtypes of NI-PHHS will be identified with the need for novel nomenclature of a heterogeneous disease entity.

Diagnosis and treatment of NI-PHHS

NI-PHHS should be suspected in adolescents or adults with new-onset HH and negative genetics and imaging for insulinoma (Witteles et al., 2001; Gupta et al., 2013). In the absence of secondary causes to adult-onset HH, targeted panel sequencing or whole genome sequencing should be performed to identify genetic causes. In the case of surgery, resection of 70-80% is considered the most appropriate surgery for NI-PHHS (Jabri and Bayard, 2004; Raffel et al., 2007). In case of persistent hypoglycemia after surgery, diet and various medical treatments including diazoxide and somatostatin analogs can be used (Yamada et al., 2020). With the improvements in the medical therapy of HH, surgery may be less often used as seen in the treatment of diffuse CHI.

Conclusion

This review provides an overview of the different histological forms of HH, their associated genetic changes, clinical characteristics, and treatment options. Histology plays, together with genetics and imaging, an important role in the diagnosis of HH, including K_{ATP}-channel diffuse or focal CHI, GCK-CHI, GLUD1-CHI, BWS-CHI, morphological mosaicism of panceatic islets, insulinoma, insulinomatosis, and NI-PHHS. Improvements in the understanding of the genotype-histotype-phenotype correlations have led to considerable progress in patient management. Intra-operative frozen section microscopy can identify a focal lesion in infants with CHI and an insulinoma in adolescent and adult HH patients, assisting the surgeon in limiting the pancreatic resection. At many centers, frozen section biopsy is performed to differentiate the different histological forms of CHI, most importantly the diffuse from the focal type. Genotype-histotype-phenotype correlations are also important in genetic counseling of families with HH.

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