The diagnosis and management of congenital and adult-onset hyperinsulinism (nesidioblastosis) – literature review

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Congenital and adult-onset hyperinsulinism (CHI) must be taken under consideration in the differential diagnosis of hypoglycaemia symptoms with endogenous hyperinsulinism, especially in cases in which there was failure to find an insulinoma. Histologic examination is necessary for a definitive diagnosis. CHI is a disorder with three histopathological variants: focal CHI, diffuse CHI, and atypical CHI. These variants are clinically indistinguishable. According to published statistics, 0.5 to 5% of nesidioblastosis cases occur in adults. Clinical manifestation ranges from mildly symptomatic up to life-threatening hypoglycaemia. Early diagnosis and treatment are important in young and very young patients because early treatment accounts for favourable mental outcomes.

Key words: congenital, adult, hyperinsulinism, nesidioblastosis, diagnosis, management.

Introduction

The term nesidioblastosis was coined by Laidlaw in 1938. He used it to describe the diffuse proliferation of cells that differentiate from the duct epithelium to build islets of Langerhans [1]. Since then the term evolved. Morphologically similar lesions are called: islet hyperplasia, endocrine cell dysplasia, islet cell adenomatosis, and ductoinsular proliferation [2, 3]. The current definition of nesidioblastosis is wider and is attributed to congenital or acquired excessive function of abnormal pancreatic β-cells resulting in persistent hypoglycaemia. Acquired nesidioblastosis is extremely rare. Nowadays the term congenital hyperinsulinism (CHI) refers to nesidioblastosis in infants.

The incidence of CHI is 1/50,000 live births (but up to 1/2500 in Saudi Arabia due to a high rate of consanguinity) [2]. Currently, 11 genes are associated with monogenic forms of CHI, as well as several genetic forms of CHI related to clinical syndrome (e.g. Beckwith-Wiedemann, Kabuki, and Turner syndromes) [4]. Genetic diagnosis is possible for approximately 50% of patients with full clinical presentation [5]. According to published data, mutations in the sulfonylurea receptor and an inwardly rectifying potassium channel are the main causes of CHI. Moreover, a link was found between gestational diabetes, diabetes mellitus, and CHI in a family carrying the inactivating ABCC8 E1506K mutation [6, 7]. In such cases the net effect is failure to reduce pancreatic insulin secretion in the presence of hypoglycaemia (serum glucose level below 60 mg/dl) [8, 9].

Clinical manifestation ranges from mildly symptomatic to life-threatening hypoglycaemia [10]. The risk of permanent brain injury in infants with CHI continues to be as high as 25-50% due to delays in
diagnosis and inadequate treatment [4]. These poor outcomes have not changed much since the 1970s despite tremendous advances in the field of understanding this condition [11]. This heterogeneous disorder leads to increased secretion of insulin from pancreatic β-cells [10, 12]. Such symptoms could be observed in neonates, predominantly shortly after birth. The panel of diagnostic methods include laboratory studies, ultrasonography, CT, MRI, PET, portal and pancreatic venous sampling, intra-arterial calcium stimulation, and microscopic examination of pancreatic tissue samples.

CHI is a disorder with three histopathological variants: focal CHI, diffuse CHI, and atypical CHI [13]. These variants are clinically indistinguishable. Surgery is the main treatment method for this disease; however, as the molecular knowledge of CHI has improved, new therapies are being developed, such as GLP-1 receptor antagonists [14], mTOR inhibitors [15], and longer-acting somatostatin analogues [16]. According to published statistics, 0.5 to 5.0% of nesidioblastosis cases occur in adults [17]. These cases are rare but well documented [18, 19, 20].

**Types of congenital hyperinsulinism**

Focal forms account for one fourth to one third of cases. They are usually restricted to a small area (2.5 to 7.5 mm in diameter) of the pancreas [2]. Due to the small size of the lesion, identification on standard imaging studies or palpation during surgery is often impossible. However, it can be simply identified by 18F-PET/CT [21, 22]. The tail and body of the pancreas are the most common locations [23]. On microscopic studies, the lesions contain clusters of large endocrine cells with characteristic giant nuclei of irregular and angular shape. Abnormal nuclei are more than 3 to 5 times the size of nearby found acinar nuclei (Figs. 1 and 2) [2]. Well-developed endoplasmic reticulum and Golgi complex (best observed on ultrastructural studies) suggest a high level of protein synthetic activity. Immunostaining shows an increased proportion of insulin-containing cells. Focal CHI does not invade the neighbour tissue nor has a pushing margins. There is no pseudocapsule. Typically, outside the focal lesion, the pancreas appears histologically and functionally normal [24]. Although most patients have a solitary lesion, one fourth of cases are multifocal [23].

Familial cases occur sporadically [25]. These have two main patterns. First is the inheritance of a paternal mutation of ABCC8 or KCNJ11. Second is the somatic loss of the maternal 11p allele involving the ABCC8 and KCNJ11 region [26]. Both result in higher proliferation of β-cells evolving into a focal adenomatous hyperplasia [27]. Focal CHI can be completely cured by surgical removal of the lesion [21, 22].

In the diffuse form of CHI, similar changes are found throughout the pancreas (Table I). All the β-cells of the islets of Langerhans are affected but the intensity of abnormalities varies throughout the organ [2, 3]. β-cells are typically enlarged because of an abundant cytoplasm. Easily visible 3–4 times larger nuclei suggests distinct hyperfunctioning [13]. Mutations in ABCC8 and KCNJ11 genes are the most common causes of diffuse CHI [28, 29]. It is worth mentioning that no changes are noted on macroscopic examination [23].

Sufficient reduction of hyperinsulinemia requires near total pancreatectomy, which in turn implicates the risk of either persistent hypoglycaemia or insulin-dependent diabetes [2, 30, 31].

Recently, a new atypical form of CHI has been characterised by morphologic mosaicism. Mosaic pattern refers to the presence of two strikingly dif-
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Different types of islets. Large islets with cytoplasm-rich \( \beta \)-cells and enlarged nuclei coexist with shrunken islets with \( \beta \)-cells showing little cytoplasm and small nuclei [32]. These hyperactive islets usually are confined to one lobe. That gives a potential chance for complete clinical symptom withdrawal after partial pancreatectomy. Hence, there is great relevance of proper diagnosis of the disease by pathologists on intraoperative frozen sections, if performed by a surgeon. In such cases the surgery would be curative [33]. In atypical form the genetic mechanism may involve mutations of GCK but it has been reported in only one patient so far [28].

Acquired adult-onset nesidioblastosis occurs mainly after Roux-en-Y gastric bypass surgery. This intervention increases levels of a \( \beta \)-cell-trophic polypeptide, such as glucagon-like peptide 1, that contribute to the hypertrophy of pancreatic \( \beta \)-cells [14]. Annual incidence of adult-onset hyperinsulinemic hypoglycaemia is 0.09/100,000 and mean patient age is 47 years [3, 18].

Diffuse changes are found throughout the pancreas with changing prevalence of localisation. On microscopic examination, enlarged or normal-appearing islets contain characteristic hypertrophic \( \beta \)-cells with pleomorphic nuclei. Endocrine cells concentrate in small, scattered clusters. Ducts forming into islets are seen as ductuloinsular complexes [18].

As in diffuse CHI, near-total pancreatectomy is needed.Performed pancreatic resections ranging from 30% to 95% of an organ have been reported so far. But because it leads to broad morphological changes type their results vary widely. Some authors suggest conservative resection with possible reoperation if appropriate glycaemic control is not achieved [23].

**Insulinoma**

In the differential diagnosis, insulinoma should definitely be taken into consideration. Insulinoma (\( \beta \)-cell tumour) occurs at the range from 1 to 4 cases/1,000,000 per year [34]. Four percent of insulinomas are associated with multiple endocrine neoplasia type 1 (MEN 1). Nevertheless, it is the most common cause of endogenous hyperinsulinism resulting in hypoglycaemia. The mean age at diagnosis is approximately 47 years with the exception of insulinoma patients with MEN 1, in whom the mean age is less than 20 years.

95% of insulinomas are benign and totally curable by complete resection. Typically, they are solitary tumours [35]. But in MEN1 patients, tumours are

<table>
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<th>CHI (Nesidioblastosis)</th>
<th>Adult Onset</th>
<th>Insulinoma</th>
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<tbody>
<tr>
<td>Age</td>
<td>&lt;1 year</td>
<td>5th decade</td>
<td>5th decade</td>
</tr>
<tr>
<td>Type of lesion</td>
<td>Benign</td>
<td>Benign</td>
<td>Mostly benign</td>
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<tr>
<td>Main localization</td>
<td>Body and tail</td>
<td>Entire pancreas</td>
<td>Entire pancreas</td>
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<td>Leading etiology</td>
<td>Sporadic</td>
<td>Genetic</td>
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<tr>
<td>Hyperinsulinemic hypoglycaemia</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Microscopic findings</td>
<td>Often unifocal</td>
<td>Diffuse with different prevalence</td>
<td>Diffuse with different prevalence</td>
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<td>Ductoinsular complexes</td>
<td>Hypertrophied ( \beta )-cells with giant nuclei</td>
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<tr>
<td>Immunohistochemistry</td>
<td>Increased number of insulin-containing cells</td>
<td>Increased number of insulin-containing cells</td>
<td>Increased number of insulin-containing cells</td>
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MEN 1 – multiple endocrine neoplasia type 1
more often multiple, and vary in size and malignant potential. They might be distributed throughout the pancreas. Surgical removal is the only curative method [34].

Although both insulinoma and CHI may present the same clinical symptoms, their morphologies differ from each other. About 80% of insulinomas are less than 2 cm in size and are solitary encapsulated tumours. They are typically large enough to be seen grossly. Extrapancreatic insulinomas are extremely rare (incidence < 2%) and occur most commonly in the duodenal wall [36]. It is worth mentioning that the size does not relate to the severity of clinical symptoms. The tumour cells contain less insulin and secretory granules than normal β-cells but have higher levels of proinsulin. β-cells may contain small amyloid depositions [37]. Atypical granules and agranular cells create solid or gyriform patterns. Insulinoma in children may be associated with nesidioblastosis (described in detail above) [38].

Final remarks

Nesidioblastosis must be taken under consideration as the differential diagnosis of hypoglycaemia with endogenous hyperinsulinism, especially in cases in which there was failure to confirm the presence of insulinoma. Nesidioblastosis can often be cured by partial or subtotal pancreatectomy. Histological examination is necessary for a definitive diagnosis. Early diagnosis and treatment are of paramount importance, especially in young and very young patients because early treatment accounts for favourable mental outcomes.

The authors declare no conflict of interest.

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