RFC10.6

Increased Islet Cell Neogenesis and Endocrine Cell Differentiation in Congenital Hyperinsulinism in Infancy

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Introduction and Objectives

Congenital Hyperinsulinism in Infancy (CHI) is characterised by inappropriate insulin release from islet β-cells. We currently attribute hypoglycaemia to β-cell dysfunction because of defects in the ion channel genes *ABCC8* or *KCNJ11.* However, the CHI pancreas is also associated with the inappropriate expression of foetal-like transcription factors and enhanced cell proliferation[1].

Hypothesis: As the CHI pancreas has a number of features in common with the foetal pancreas, we hypothesised that islet cell differentiation and neogenesis (figure 1) would also be enhanced in disease.

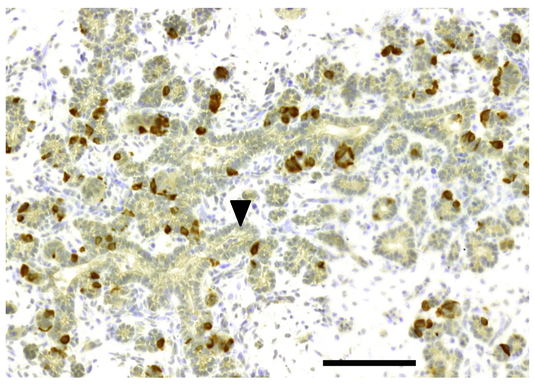


Fig. 1. Islet cell neogenesis and differentiation in the developing human pancreas. Note the high incidence of ducal structures (triangle) in the developing human pancreas at 11 weeks post-conception (wpc). Single islet cells (Ins$^+$) and islet-like clusters clearly seen amongst the ductal cells. Scale bars represent 10 µm.

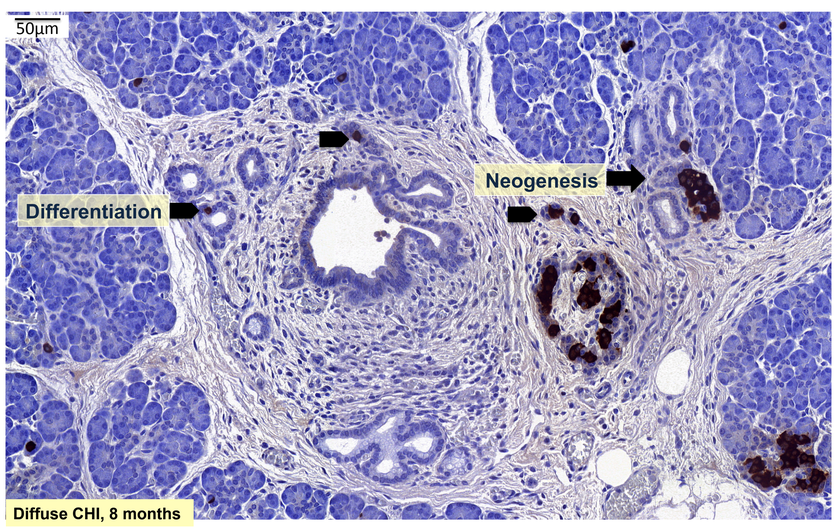
1. Salisbury et al., *Diabetes* (2015) 64:3182–3188).

Methods

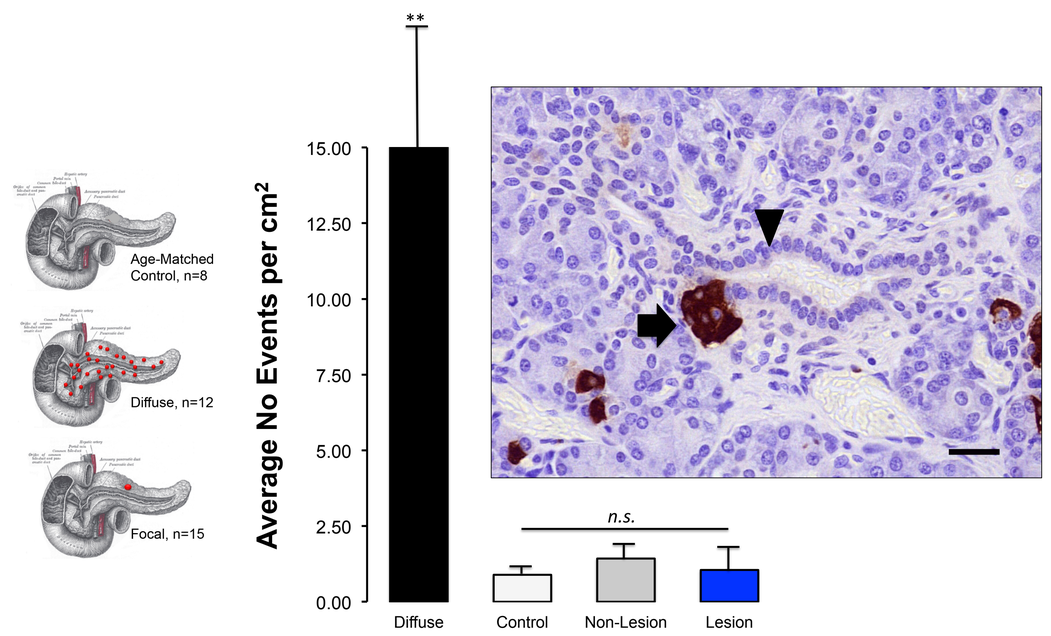
Pancreatic tissue was obtained from 25 patients with CHI following surgery. All patients were positive for *ABCC8* or *KCNJ11* gene defects. Twelve patients had diffuse-CHI (age: 2-13 months at surgery) and 13 patients had focal disease (age: 1-10 months at surgery). Tissue samples were fixed and processed for use in immunohistochemical analysis. Quantification of both single insulin-expressing cells (Ins$^+$) within ductal epithelia (a marker of differentiation) and islet cell clusters associated with ducts (neogenesis) was carried out and normalised to the area of the tissue section. Control data was obtained from foetal tissue (n=6, 11-13 wpc) or from age-match pancreata following post-mortem (n=8, 1-12 months).

1: Islet Neogenesis and Endocrine Cell Differentiation

In diffuse CHI tissue, single Ins$^+$ cells were seen with ductal epithelia cells at all ages and islet cell clusters found associated with or emerging from the ducts; neogenesis.

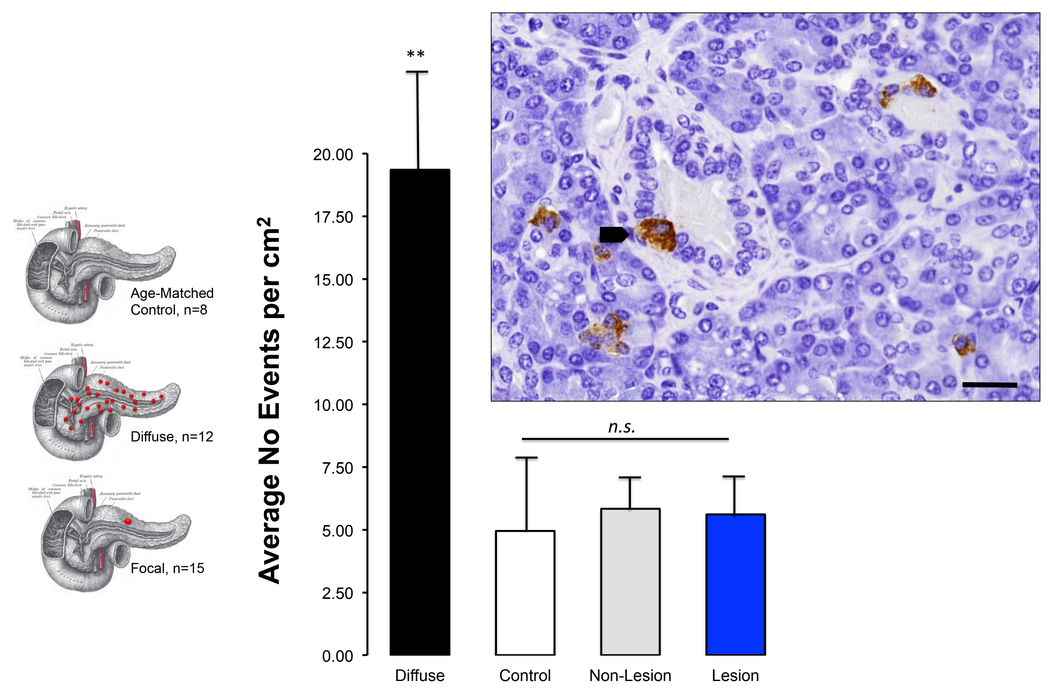


2: Enhanced Islet Neogenesis in Diffuse CHI



The incidence of islet neogenesis was markedly increased in diffuse CHI disease (arrow, scale bar 25 µm) compared to control tissue; 15.2 ± 3.8 events/cm^2 (n=12) vs. 0.89 ± 0.3 events/cm^2 (n=8). This was independent of *ACCB8/KNCJ11* defects as no differences were found in the incidence of neogenesis in focal CHI tissue; 1.1 ± 86 vs. 1.4 ± 0.6 events/cm^2 in lesion and non-lesion domains, respectively (n=15). Duct indicated by arrow.

3: Islet Cell Differentiation is Enhanced in Diffuse CHI



Islet cell differentiation from ductal progenitor cells was markedly elevated in incidence in diffuse CHI disease (arrow, scale bar 25 µm) compared to controls; 19.4 ± 4.4 events/cm^2 (n=12) vs. 4.9 ± 2.9 events/cm^2 (n=8). This was independent of *ACCB8/KNCJ11* defects as no differences were found in the incidence of stem cell differentiation in focal CHI tissue; 5.4 ±1.6 vs. 5.1 ± 1.4 events/cm^2 in lesion and non-lesion domains, respectively (n=15)

Summary / Implications

Diffuse CHI is associated with a 17-fold increase in the incidence of islet cell neogenesis (nesidioblastosis) and a 4-fold increase in the incidence of islet cell differentiation from duct progenitors. This suggests a remarkable degree of endocrine cell plasticity in the post-natal pancreas of diffuse CHI patients.

Summary / Implications

The enhanced incidence of neogenesis and differentiation is not found in focal CHI tissue. This suggests that *ABBC8/KCNJ11* defects in progenitor cells – rather than elevated insulin levels, are likely to be responsible for inappropriate increases in new islet cell formation in CHI .

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