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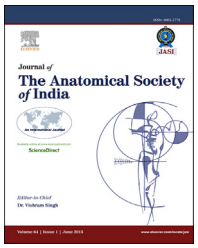

Original Article

Prenatal development of the human endocrine pancreas: A morphological and immunohistochemical study

Swati Tiwari, Sabita Mishra[*], *J.M. Kaul*

Department of Anatomy, Maulana Azad Medical College, New Delhi 02, India

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ABSTRACT

Introduction: The endocrine pancreas plays a pivotal role in glucose metabolism. As regards the morphogenesis of the islets of Langerhans, there is conflicting data regarding the timing of appearance of the B cells, and, the proportion and arrangement of the B cells within the islets. The present work is a baseline study conducted in the Indian subcontinent. The histogenesis of the islets of Langerhans was studied and we also observed the expression of anti-insulin antibody in the islets at different gestational ages.

Methods: Ten aborted fetal specimens of pancreas of gestational ages 10–36 weeks were procured from the Department of Obstetrics and Gynaecology, LNJP Hospital, New Delhi. Fetuses were fixed in 10% formalin. Serial sections were stained with Haematoxylin and Eosin and few sections were processed for immunocytochemistry with a specific marker for B-cell, the anti-insulin antibody.

Results: The cells of the islets arise from the lining epithelium of the tubules. The B cells contain insulin at 10th week as seen by immunostaining. Small capillaries are seen enclosed in the islets at 14 weeks. The arrangement of B cells in different islets is variable. The formation of islets continues throughout fetal life.

Discussion: Our study reaffirms that the endocrine pancreas begins to differentiate early in fetal life. The growth and maturation of islets is associated with coordinated vascular development. By the 28th week of intrauterine life, the fetal pancreas attains sufficient morphological maturity so as to fulfil the hormonal requirements of the growing fetus.

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1. Introduction

The islets of Langerhans, the endocrine component of the pancreas, are complex micro-organs involved in glucose homeostasis. Seven different types of cells have been found in the islets – A, B, D, F, D_1, EC (enterochromaffin cells), G1 (gastrin) cells. The B cells are the most common and account for 60–75% of the cells in the islets.[1] B cells mainly secrete

* *Corresponding author*. Tel.: +91 9968604206.
E-mail address: sabitamishra12@gmail.com (S. Mishra).

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insulin and islet amyloid polypeptide (IAPP).[2] Insulin plays a key role in glucose metabolism. Deficiency of insulin results in diabetes mellitus. Research has shown that pathological changes occur in the pancreas especially in the islets in diabetes mellitus. Diabetes mellitus is the most common metabolic disorder affecting millions worldwide. India has the highest number of estimated cases of diabetes in the world.[3] Type 1 diabetes or Insulin Dependent diabetes patients need a regular external replenishment of insulin in order to lead a normal life. Diabetes can also occur as early as first six months of life known as monogenic diabetes. Research shows that in diabetics, pathological changes occur in the pancreas especially in the islets.[4,5] Thus, the embryogenesis and renewal of the islets is of critical importance in diabetology. A detailed knowledge of the normal development of the islets will help in understanding any developmental anomaly that may trigger the pathogenesis of diabetes. There are many such developmental studies in lower mammals and invertebrates. But, there are wide interspecies differences between the islets of humans and other mammals.[6,7] Hence, data from studies on lower mammals cannot be extrapolated onto humans. This also explains why treatment modalities for diabetes which were found successful in rodents did not produce similar results in humans. Factors that affect islet cell development in the higher mammals, especially human pancreas are not well known. There are some human studies but they show variation in the data regarding the time of appearance of hormone containing B cells. Hence, we have taken up this study to understand the embryogenesis of pancreas, especially the endocrine component, in humans in the Indian subcontinent. It is a baseline study of the sequential development of the parenchyma with particular focus on the histogenesis of the islet cells.

2. Materials and methods

Fetuses of gestational age 10–36 weeks were procured from the Department of Obstetrics and Gynaecology, L.N.J.P. Hospital, New Delhi after obtaining approval from institutional ethical committee of Maulana Azad Medical College and associated L.N.J.P. Hospital. Informed consent of parents was taken and patient anonymity was preserved. Fetuses below the gestational age of 20 weeks were obtained from abortions conducted in accordance with the Medical Termination of Pregnancy act, while those above 20 weeks of gestation were obtained from stillbirths. A detailed maternal history was recorded and diabetic mothers were excluded from the study. Patient anonymity was preserved. An initial assessment of the fetus was done to rule out any gross abnormality. Only normal fetuses were included in the study. The gestational ages of the procured fetuses was determined by measuring- Crown-Rump length, Crown-Heel length, Bi-parietal diameter and Foot Length.

Incision was given longitudinally on the anterior abdominal wall in the median plane for better penetration of the fixative into the abdomen. The fetus was then immersed in 10% paraformaldehyde. After fixation, the pancreas was dissected out and preserved in fresh fixative for 1–2 weeks. The specimens were labelled and processed for paraffin embedding. 7 μm thick serial sections were generated on a rotary microtome with the long axis of pancreas as the cutting surface.

3. Staining

Sections were stained with haematoxylin and eosin (H&E) stain to see the morphology of the developing pancreas. In each fetal pancreas, few sections were processed for immunohistochemistry (IHC). Deparaffinised sections were incubated in citrate buffer and the endogenous peroxidase activity was blocked using methanol and 1% H_2O_2. After washing with working solution of phosphate buffer with 0.1% Triton X, slides were treated with normal horse serum for 2 h for blocking the non specific antigen. The sections were then incubated with monoclonal anti-insulin antibody at a dilution of 1:200, at 4 °C overnight. Slides were then treated with biotinylated secondary antibody, and the reaction was observed using diaminobenzidene as chromagen.

All stained sections were assessed qualitatively under the BX 61 computerised microscope and the images were captured with Olympus DP71 camera. Processing of images was done using the Image Pro plus MC 6 software. The B cells, stained for anti-insulin antibody were observed and analysed.

4. Results

10 weeks: At this gestational age, the dorsal and ventral pancreatic buds had already fused to form one single mass. A thin connective tissue capsule was seen around the gland. The parenchyma of the gland at this stage consisted of large amounts of mesenchymal tissue with an interspersed network of branching tubules. The tubules were lined by columnar epithelium with cells having a lightly eosinophilic cytoplasm and oval vesicular nuclei present towards the base. The nuclei had a prominent nucleolus. It was difficult to distinguish between the cells in the terminal tubules and the primitive acinar cells (Fig. 1a). Immunostaining revealed that few cells in the lining of tubules showed a positive reaction with anti-insulin antibody, thus confirming the presence of B cells in the lining of the tubules (Fig. 1b).

14 weeks: By the 14th week, the parenchymal tissue had started organising into vaguely defined lobes. The parenchyma contained branching tubular ducts lined by columnar to stratified epithelium. Cells were budding out from the tubules especially from the stratified areas in the form of cords and small clusters. Many islets were in the stage of budding out from the tubules. The developing islets were enclosing more and more capillaries within them. Some islets had detached from the tubules and were seen in close proximity to the tubules. These were mostly small islets with few scattered loosely packed cells (Fig. 2a). Immunostaining showed many more insulin-positive B cells in each section at this age. The cells were more intensely stained than in younger fetuses. There were single B cells present in the lining of tubules. B cells were also seen in the budding out islets. Very few large islets were seen in the tail region of the pancreas (Fig. 2b). In

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