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Chronologic Developmental Histology of Human Adrenal Medulla

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Abstract

Development of human adrenal medulla has always been a topic of quandary because of insufficient literature. Most of the studies on adrenal medulla pertain to various species of animals but human fetuses. This research work emphasizes on the developmental chronology of events by studying 36 human fetal adrenal medullas. This study confirms that neural crest derived sympathoblasts migrate through the cortex into the medulla at 12 weeks as opposed to the prevalent view of 8 weeks in animal studies. Cortical and medullary differentiation begins at 12 weeks of gestation and is complete by 16 weeks. Medullary sinusoids appear at 16 weeks. Adrenaline and noradrenaline secreting cells are separate entities and they differentiate from the chromaffin cells at 22 weeks. Moreover ganglionic cells are seen in the medulla for the first occasion at 22 weeks. It is imperative to understand the human medullary differentiation in order to shed light on emerging diseases due to developmental anomalies of adrenal medulla.

Keywords: Adrenal Medulla; Sympathoblasts; Chromaffin Cells; Sinusoids; Ganglionic Cells.

Introduction

The adrenal medulla is a chief neuroendocrine gland which mediates the stress response in humans by secreting catecholamines especially epinephrine. In addition it also secretes a cocktail of bioactive substances like neuropeptides, encephalins, cytokines and neurotrophic factors [1,2]. Fetal adrenal glands are comparatively large consistent with its endocrine capabilities. Adrenal medulla is composed of glial cells, ganglion cells and chromaffin cells, all of which are derivatives from neural crest cells [3,4]. Sympathoadrenal (SA) progenitor cells and other medullary precursor cells derived from the lumbar neural crest migrate through the fetal adrenal cortex as early as 6-8 weeks of gestation [5] although certain authors have reported that the glial cells do not appear in the adrenal gland till 20th week of intra-uterine life [6]. SA cells later differentiate into ganglion and chromaffin cells. Non chromaffin cells of the adrenal medulla include connective tissue cells and endothelial cells which invest clusters and rosettes of chromaffin cells in a fenestrated capillary network and are diverse anatomically from the adrenal sinusoids [7,8]. There has been a paucity of observations regarding the appearance and migration of these medullary cells through the fetal adrenal cortex into the central medulla. Likewise there is very little information in the literature whether these cells are responsible for the destruction of the fetal cortex while their invasion. The aim of this study was to investigate the chronological pattern of migration of the chromaffin cells through the fetal adrenal gland and their aggregation in the medullary region.

Materials and Methods

Thirty six human fetuses (20 males, 16 females) with gestational age ranging from 8 weeks to 22 weeks (CRL 36mm to 240mm) were examined. These still born fetuses were donated to the department of Anatomy for research purposes with the agreement of the families concerned. The age of the fetuses was calculated taking into consideration different factors like maturity, mother's menstrual history and crown rump length (CRL). All fetuses were normal on examination with no apparent signs of any

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developmental anomalies. Adrenal glands were dissected out bilaterally from all the fetuses and fixed in 10% formalin solution. After proper tissue processing adrenal specimens were embedded in paraffin wax and 6µm sections were taken for preparation of histological slides with haematoxylin and eosin stains.

Results

General Appearance

The adrenals become an apparently visible neuroendocrine organ by 8th week of gestation and hence were clearly visible in all the fetuses covered by an inconstant capsule. The weight of the gland gradually increased from 8th to the 22nd week of gestation ranging from 0.4 gms at 8weeks to a maximum of 2.0 gms at 22 weeks. There was no significant difference in the weight of the right and left adrenals belonging to fetus of either sex. The adrenals were approximately the size of the corresponding kidneys at 22nd week. Transverse sections of the adrenals revealed a highly vascular central core and a comparatively less vascular, pale peripheral cortical rim.

Vasculature

Variable numbers of adrenal arteries were seen during gross dissection of the fetuses. Most of them took origin from the embryonic dorsal aorta. Fetuses in the later stages of gestation also showed adrenal arteries originating from variable sources especially renal arteries. An ill formed sub-capsular plexus was seen in most of the fetal adrenal glands in histological sections. These sub capsular plexuses were seen to give rise to multiple numbers of medullary arterioles to supply the human fetal adrenal medulla. Density of the cortical and medullary sinusoids increased with increasing fetal age.

Microscopic Appearance of Fetal Adrenal Medulla

8 weeks (Fig. 1A): An undifferentiated mass of adrenal cells is present. The cells stain pale with haematoxylin and eosin. Fetal adrenal cortical cells and sympathoblasts/chromaffinoblasts are not histologically distinct. Differentiation between cortex and medulla is not possible.

12 weeks (Fig.1B & 1C): Cortex begins to differentiate and numerous eosinophillic cortical cell masses can be easily identified. Interspersed and migrating through these cortical cells are highly darkly stained sympathoblasts which are derived from the migrating neural crest cells. These sympathoblasts will differentiate into chromaffin and non-cromaffin cells of the medulla in later stages of gestation. Later stages of 12 week fetus reveal the differentiation of fetal adrenal medulla into loose connective tissue (medullary parenchyma) and chromaffin cells. Newly differentiated chromaffin cells have pale staining irregular morphology with pyknotic nuclei. A very significant observation is that medullary sinusoidal capillaries are not developed at this stage.

16 weeks (Fig. 1D): Cortex and medulla are completely differentiated. Chromaffin cells now have

Light-micrograph of the medulla of suprarenal gland (H & E stain)

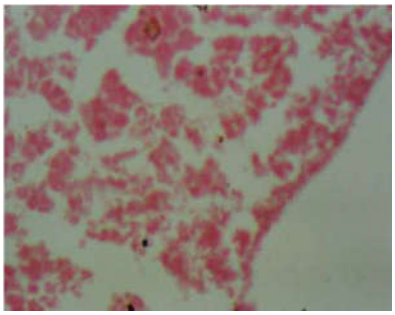

Fig. 1a: 8 weeks: cortex & medulla not differentiated 100x

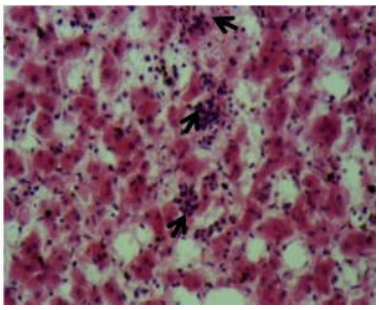

Fig. 1b: 12 weeks: collection of undifferentiated cells (arrow) & scattered cells of the cortex 200x

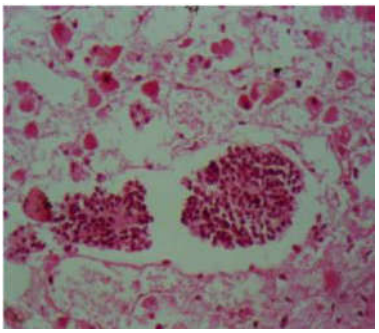

Fig. 1c: 12 weeks: collection of undifferentiated cells & loose connective tissues & scattered cells of the medulla 200x

a regular, pale staining and more distinct appearance. Medullary sinusoidal capillaries can easily be seen. Examination under high magnification reveals that chromaffin cells are in close association with the endothelial cells of the sinusoids. This explains and confirms the endocrine nature of these cells and the activation of sympatho-adrenal system at 16 weeks of gestation. Ganglionic cells have not yet appeared in the fetal adrenal medulla. Moreover, chromaffin cells do not show any delineation into adrenal or nor-adrenal secreting types.

22 weeks (Fig.1E, F & G): Most significant observation

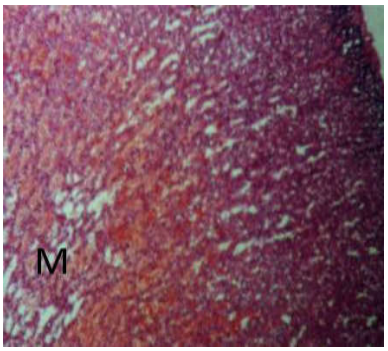

Fig. 1d: 16 weeks: development of medulla showing large number of sinusoidal capillaries 100x

at this stage of gestation is the differentiation of chromaffin cells into adrenaline secreting cells (ASC) and nor-adrenaline secreting cells (NASC). ASCs are large light staining cells with pale staining nuclei. NASCs are large light staining cells with dark staining nuclei. Cytoplasm of both the cells appears to be rough in nature signifying the presence of secreting granules in both the cells. Another significant finding at this stage is the appearance of clumps of sympathetic ganglionic cells. These ganglionic cells are seen to have dark staining, round nucleus with scantily stained cytoplasm. It's important to notice that these cells do not show any peripheral processes like axons and dendrites (Figure 1).

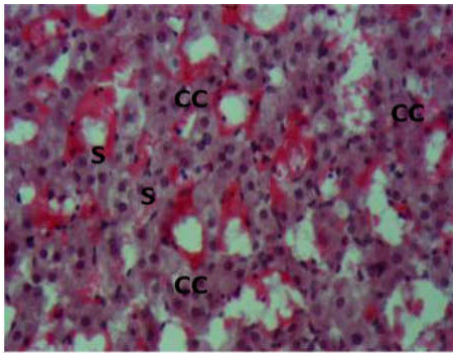

Fig. 1e: 22 weeks: the chromaffin cells (CC) & sinusoides (s) are present 200x

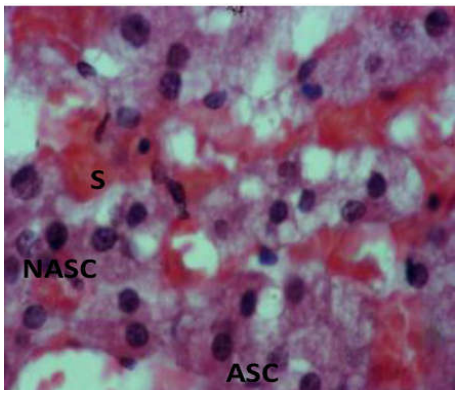

Fig. 1f: 22 weeks: Adrenaline (ASC, pale appearance) and non adrenaline secreting cells (NASC, dark appearance) 400x

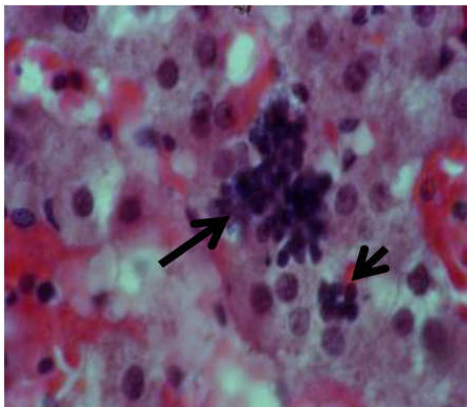

Fig. 1g: 22 weeks: collection of sympathetic ganglion cells (arrow) along with both types of chromaffin cells 400x

Discussion

Extensive comparative analysis of the development of human adrenal medulla is intricate for the authors of this research because of paucity of literature on embryological development of human medulla. Most of the research work in literature on adrenal medulla has been performed on various animals and that too concentrating on adrenal cortical development. This study shows that the adrenals become an apparently visible structure at 8th week of gestation and attain the size of the corresponding kidney at a later stage of 22nd weeks of gestation. Keene and Hewer [9] on the other hand reported that at 6 weeks the gland is a clearly defined organ situated on the upper pole of the kidney and by 8 weeks its maximum cross-section equals that of the kidney. We confirm the presence of a highly vascular central core and a comparatively less vascular, pale peripheral cortical rim as also reported by Keene and Hewer. The gland

shows a steady increase in weight throughout fetal life and regresses in size after birth. Our study showed that on an average the adrenals weighed 0.4 gms at 8 weeks and 2.0 gms at 22 weeks of gestation. Keene and Hewer reported a similar weight ratio in the initial weeks of gestation but charted a much lower weight of 1.0 gm at 22 weeks of gestation. This might be possible because of varying fetal weights due to environmental, maternal and genetic differences. Keene and Hewer reported that the sympatho-chromafil elements can easily be distinguished at 8 weeks of gestation with a positive chromaffin reaction at 22 weeks. They suggested that these cells can be seen invading the adrenal cortex at 8 weeks. Two types of these cells were recognized and accompanying nerve fibers were also sometimes seen. The more numerous of the two types of cell were small with a darkly staining nucleus and very little protoplasm; possibly these were neuroblasts. The second type of cell was larger than the neuroblast and had a vesicular nucleus but was considerably smaller than the cells of the foetal cortex. These were the so called para-sympathetic cells. Both types of cell persist throughout foetal life, and are the precursors of cells (other than large ganglion cells) found in the post-natal medulla. Our study on the contrary suggests that sympathoblasts derived from the migrating neural crest cells can first be identified only at 12 weeks of gestation and that they differentiate into chromaffin and non-chromaffin elements during the late stages of the 12th week. Zuckerkandl [10] on the contrary suggested that the human adrenal medulla is entirely developed from a single type of sympathetic anlage. This study confirms the presence of sympathetic ganglionic cells only at a very late stage of 22 weeks of gestation. We also confirm that chromaffin cells differentiate into two cellular elements only at 22nd week namely ASCs and NASCs. This research work did not find any evidence to confirm the reporting of Cooper [11] suggesting that the sympatho-chromophils gave rise to the ganglionic cells as they invaded the medulla.

Conclusion

This study defines the development of different elements of human adrenal medulla chronologically. We provide allometric data from a considerable number of human fetuses which will aid in histological and ultrasonographic studies of the adrenal gland in future. It is imperative to have precise knowledge of adrenal medullary development to correctly diagnose and manage adrenal developmental anomalies in new born infants.

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