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ORIGINAL ARTICLE

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Age-related distribution of endocrine cells in the human prostate: a quantitative study

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Abstract A morphometric analysis was performed to obtain quantitative data on age-related changes in prostatic endocrine cell (PrEC) density. Sixty prostates from subjects aged 14–74 years were studied with a semi-automatic image analysis system (ASM 68K, Leitz) applied to sections immunostained for chromogranin A-reactive cells. The highest density of PrECs (0.366 cells/mm of epithelial length) was found in the 25–54 year age group, which was significantly different from that found in prostates of the younger (0.311 cells/mm) and the older (0.261 cells/mm) age groups. The data probably reflect the higher incidence of incompletely developed glandular units in the younger group and the formation of new alveoli related to the usual glandular hyperplasia that occurs with increasing age in the older group.

Key words Normal human prostate · Endocrine cells Morphometry

Introduction

Prostatic endocrine cells (PrECs) have been observed in various age groups in normal, benign hyperplastic and neoplastic prostate (Pretl 1944; Capella et al. 1981; di Sant'Agnese et al. 1985; Abrahamsson et al. 1987; di Sant'Agnese and de Mesy Jensen 1987; di Sant'Agnese 1992; Oesterling et al. 1992). On qualitative morphological observations, age-related variations of the endocrine cell incidence are not apparent in normal or hyperplastic human prostate (Abrahamsson et al. 1987). Nevertheless di Sant'Agnese et al. (1985) observed a more pronounced focal distribution of PrECs with increase in periurethral ducts and acini and decrease in peripheral acini in prostates from what they called an older population. However, these findings must be interpreted cautiously as they included prostates from patients who had received irradiation for bladder carcinoma.

Quantitative studies on guinea pigs showed a significant age-related increase in PrECs (di Sant'Agnese et al. 1987). There is no quantitative analysis of the age-related occurrence of PrECs in Man and we therefore evaluated the age-related incidence of PrECs in the epithelial lining of the alveoli and secondary ducts of the normal human prostate. We wished to identify a baseline trend of PrEC density throughout a wide range of adult life.

Materials and methods

Large samples of selected prostate glands without obvious gross or microscopic lesions, obtained from 60 subjects aged 14–74 years who had been killed in road accidents, were examined after 10% calcium acetate formalin (pH 7) fixation and paraffin embedding. Histological sections 7 μm thick were stained with haematoxylin and eosin and Verhoeff-van Gieson. In every case, sections for immunocytochemistry were processed with monoclonal antibodies to chromogranin A (ChrA; Dako), which is a sensitive marker of neuroendocrine cells (Abrahamsson et al. 1989). A brown-coloured final product was developed using an avidin-biotin immunoperoxidase reagent.

The morphometric study was carried out using a Leitz ASM 68K semi-automatic image analysis system, connected to the microscope. The glandular profiles were traced out onto the digitizer board to measure the length of their epithelial lining. Tracings were made along the basal lamina of alveoli and ducts. While performing measurements, the amount of ChrA-positive cells present in the profiles was recorded.

Several groups of alveoli were chosen at random, to avoid bias due to the patchy distribution of PrECs. The overall length of epithelial profiles traced for each case was at least 300 mm. The measurements proved to be readily reproducible.

The linear density of ChrA-positive cells was calculated and expressed as the number of cells per millimetre length of epithelial

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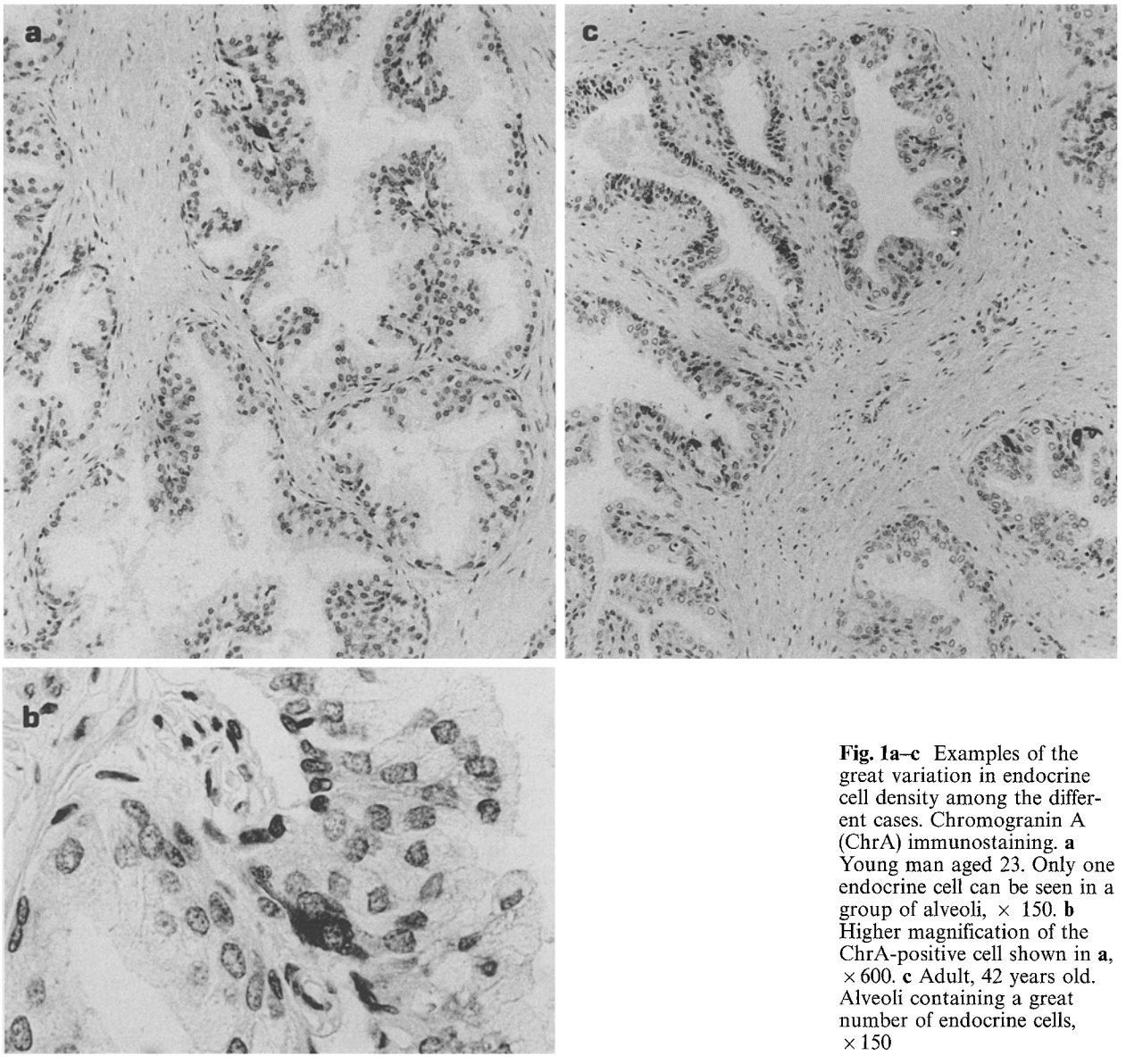

Fig. 1a–c Examples of the great variation in endocrine cell density among the different cases. Chromogranin A (ChrA) immunostaining. **a** Young man aged 23. Only one endocrine cell can be seen in a group of alveoli, × 150. **b** Higher magnification of the ChrA-positive cell shown in **a**, × 600. **c** Adult, 42 years old. Alveoli containing a great number of endocrine cells, × 150

lining. The data obtained were then subjected to statistical analysis by Fisher's *F*-test and Student's *t*-test.

Results

The density of PrECs showed a marked variation (Fig. 1) from case to case (ranging between 0.083 and 0.684/mm) with a general increase with age up to about the fifth decade, and thereafter a decline (Fig. 2).

In order to analyse the age-related variations, cases were grouped into age intervals of 10 years as follows: under 15 years; 15–24; 25–34; 35–44; 45–54; 55–64; 65 years and over. The mean densities found in each group are listed in Table 1. The highest values of the counts were found in the age groups 35–44 and 45–54 years. The statistical significance of the differences between these groups and the other ones was assessed by applying the Student's *t*-test; the results are summarized in Table 2. Significant differences were only found in the comparisons of the youngest (15–24 years) and elderly (55–64 years) groups. The comparison with the oldest group (65 years and over) shows no significant difference, but the number of cases in the group is too small to make the evaluation reliable.

Despite the large variation observed among cases of the same age group or even of the same age, the statistical analysis appears to confirm the trend observed in Fig. 2, with a concentration of the cases showing higher endocrine cell density in the age range comprising the third, fourth and fifth decades.

Thus statistically three main age groups may be identified: A (14–24 years); B (25–54 years); C (55 years and over). As shown in Table 3, the number of PrECs per unit length of epithelium is higher in group B than in groups A and C, with significant and highly significant

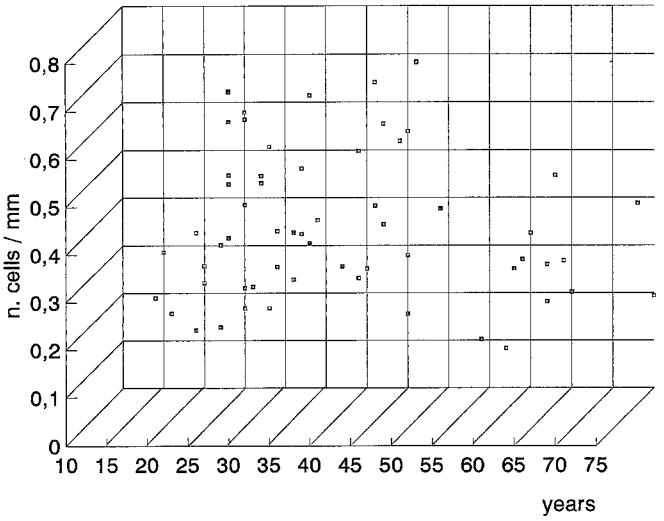

Fig. 2 Plot of the density of prostatic endocrine cells (ChrA-positive cells) against age

Table 1 Number of prostatic endocrine cells (PrECs) per millimetre of gland epithelium length. The mean and the standard error of the mean (*SEM*) are given for each age group

Age (years)	Number of cases	Mean	SEM
<15	1	0.286	
15–24	13	0.313	0.152
25–34	19	0.332	0.194
35–44	9	0.408	0.140
45–54	7	0.402	0.219
55–64	8	0.261	0.134
≥65	3	0.261	0.087

Table 2 Significance of the *t*-test applied in the age group evaluations shown in Table 1 (*NS* not significant)

Age (years)	35–44	45–54
15–24	<0.005	<0.05
25–34	NS	NS
35–44		NS
45–54	NS	
56–64	<0.001	<0.02
65–74	NS?	NS?

Table 3 PrEC density (cell number/mm epithelium) in three main age groups

Group	Age (years)	Number of cases	Mean	SEM	*t*-test	*P*
A	<25	14	0.311	0.146		
					2.894	<0.01
B	25–54	35	0.366	0.192		
					4.772	<0.001
C	≥55	11	0.261	0.122		

differences respectively. The reliability of the Student's *t*-test is supported by the evaluation of *F* for the analysis of variance, since the Fisher's test indicates that groups can be considered to have the same variance ($P > 0.05$).

Table 4 Trend of PrEC density in the three main age intervals slightly different from those in Table 3

Age (years)	Number of cases	Mean	SEM	*t*-test	*P*
≤20	7	0.222	0.062		
				6.538	<0.001
21–50	41	0.392	0.152		
				9.06	<0.001
≥51	12	0.247	0.125		

The differences between the 20–50 years group and the younger and elderly ones remain highly significant when the age boundaries of groups are slightly modified, as shown in Table 4.

Discussion

Our results indicate variations of PrEC density from younger to older subjects, with a peak in the central age group (Tables 3, 4). It is interesting to note the low counts recorded in the older age group, a finding in contrast with data obtained in guinea pigs by di Sant'Agnese et al. (1987). They found that the number of PrECs per unit length did not differ in weanlings (9 days) or in mature pre-breeders (11–12 weeks), but showed a roughly 24-fold increase in the older animals (the retired breeders). However, even if a similar age grouping criterion cannot be applied in Man, the retired breeders resemble our adult age group, which showed a significant increase in mean PrEC density. A real counterpart of our old age group cannot be found in the experimental design of di Sant'Agnese and coworkers. Qualitative observations on human prostates obtained from radical cystectomies ascribed a decreased number of PrECs in the peripheral acini to "incidental... irradiation, prostatic pathology or simply old age" (di Sant'Agnese et al. 1985).

However an age-related decrease in the number of endocrine cells has been reported in human organs, such as stomach (Takahashi et al. 1980; Green et al. 1986, 1989) and appendix (Shaw 1991). This has been related to involution (Takahashi et al. 1980) but the real causes are not known.

In our view, the lower density of PrECs we observed in the younger age group when compared with middle-aged men could be explained by the fact that many glandular units are not completely developed (Battaglia 1989a). In the older group the lower density of PrECs depends on the growth of new alveoli derived from microglandular clusters (Battaglia 1989b, 1991). Those new glandular subunits tend to increase the bulk of prostatic alveoli in old age. Preliminary observations suggest that PrECs are very scanty both in newly formed alveoli and in microglandular clusters. However, additional studies are needed to fully explain the age-related fluctuation in the tissue density of endocrine cells in the prostate.

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References

Abrahamsson PA, Alumets J, Waldstrom L, Falkmer S, Grimelius L (1987) Peptide-hormone- and serotonin-immunoreactive tumour cells in carcinoma of the prostate. In: Murphy GP, Khoury S, Kuss R, Chatelain C, Denis L (eds) Prostate cancer, part A. Research, endocrine treatment, and histopathology. Liss, New York, pp 489–502

Abrahamsson PA, Falkmer S, Falt K, Grimelius L (1989) The course of neuroendocrine differentiation in prostatic carcinomas. An immunohistochemical study testing chromogranin A as an "endocrine marker". Pathol Res Pract 185:373–380

Battaglia S (1989a) Classification of prostate atrophy. In: Karr JP, Yamanaha H (eds) The second Tokyo symposium on prostate cancer. Elsevier, New York, pp 148–160

Battaglia S (1989b) Epithelial hyperplasia of the prostate gland. In: Karr JP, Coffey DS, Gardner W (eds) Prognostic cytometry and cytopathology of prostate cancer. Elsevier, New York, pp 122–137

Battaglia S (1991) Histogenesis of incidental carcinoma of the prostate. In: Altwein J, Faul P, Schneider W (eds) Incidental carcinoma of the prostate. Springer, Berlin Heidelberg New York, pp 63–73

Capella C, Usellini L, Buffa R, Frigerio B, Solcia E (1981) The endocrine component of prostatic carcinomas, mixed adenocarcinoma-carcinoid tumours and non-tumour prostate. Histochemical and ultrastructural identification of the endocrine cells. Histopathology 5:175–192

Green DM, Bishop AE, Rees H, Polak JM (1986) ECL cell population in normal human fundus (abstract). J Pathol 148:115

Green DM, Bishop AE, Rindi G, Lee FI, Daly MJ, Domin J, Bloom SR, Polak JM (1989) Enterochromaffin-like cell populations in human fundic mucosa: quantitative studies of their variations with age, sex and plasma gastrin levels. J Pathol 157:235–241

Oesterling JE, Hauzeur CG, Farrow GM (1992) Small cell anaplastic carcinoma of the prostate: a clinical, pathological and immunohistological study of 27 patients. J Urol 147:804–807

Pretl K (1944) Zur Frage der Endokrinie der menschlichen Vorsteherdrüse. Wirchows Arch 312:392–404

Sant'Agnese PA di (1992) Neuroendocrine differentiation in carcinoma of the prostate. Cancer [Suppl] 70:254–268

Sant'Agnese PA di, Mesy Jensen KL de (1987) Neuroendocrine differentiation in prostatic carcinoma. Hum Pathol 18:849–856

Sant'Agnese PA di, Mesy Jensen KL de, Churukian CJ, Agarwal MM (1985) Human prostatic endocrine-paracrine (APUD) cells. Distribution analysis with a comparison of serotonin and neuron-specific enolase immunoreactivity and silver stains. Arch Pathol Lab Med 109:607–612

Sant'Agnese PA di, Davis NS, Chen M, Mesy Jensen KL de (1987) Age-related changes in the neuroendocrine (endocrine-paracrine) cell population and the serotonin content of the guinea pig prostate. Lab Invest 57:729–736

Shaw PA (1991) The topographical and age distributions of neuroendocrine cells in the normal human appendix. J Pathol 164:235–239

Takahashi T, Shimazu H, Yamagishi T, Tani M (1980) G cell populations in resected stomachs from gastric and duodenal ulcer patients. Gastroenterology 78:498–504