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Weight and Shape of the Human Adrenal Medulla in Various Age Groups

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Summary. The weight and shape of the adrenal medulla were studied in 118 adrenal glands obtained at autopsies of 62 patients (38 males and 24 females) between 0 and 52 years of age. In adolescents 15 years and older and adults cases of sudden death only were entered in this study. The weight was calculated using morphometric measurements done on serial sections of the glands. In the new-born, the medulla accounts for less than 1% of the total volume of the adrenal gland. Though there is a rapid growth of the adrenal medulla after birth, the percentage of adrenal medullary volume at all age levels during childhood and adolescence is lower than in adults where it constitutes 9% of the total adrenal volume on the average. This corresponds to an average medullary weight of 0.43 g. In the new-born, the medulla consists of a thin plate made up of immature medulloblasts. Within a few months these are transformed into mature medullary cells; the shape of the medulla soon approaches that of the adult gland: an increase in thickness around the central vein and flat processes into the alae. With increasing age the cortico-medullary border becomes irregular and ragged. Especially in the vicinity of the central vein an intermingling of medullary and cortical cell complexes is found. An unequivocal diagnosis of genuine adrenal medullary hyperplasia can be established only by weighing the dissected medulla or by applying morphometric methods.

Key words: Adrenal medulla – Weight and shape – Ageing

Introduction

Rarely, a phaeochromocytoma is discovered to be the cause of arterial hypertension. There have also been reports stating, that not only this circumscribed neoplasm but also diffuse hyperplasia of the adrenal medulla may lead to hypertension (Liebegott 1952; Montalbano et al. 1962; Rudy et

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al. 1980). Hyperplasia can only be recognized when the normal weight is known. However, few studies dealing with the weight of the human adrenal medulla have been published. Quinan and Berger (1933) determined the weight of both adrenals in 50 persons between 17 and 62 years of age on whom a medico-legal autopsy had been performed. They weighed the adrenal medulla after dissecting away the adrenal cortex. Other authors employed morphometric methods (Hammar 1924; Swinyard 1940 and 1943; Liebegott 1952; De Lellis et al. 1976; Rudy et al. 1980). In all these studies comparatively few cases were evaluated. Furthermore, the majority of these glands were from patients who had died of chronic diseases, frequently tuberculosis. The values thus obtained therefore may not necessarily represent the normal weight. Several studies dealing with the total weight of the adrenal gland have demonstrated (Materna 1941; Spann and Heinemann 1955; Kreiner and Dhom 1979) that the average weight of adrenal glands from healthy persons who had died suddenly (in accidents) is distinctly lower than that of an unselected autopsy population. It thus appears worthwhile to study the weight and shape of the human adrenal medulla in a larger number of persons of different ages. An attempt was made to use organs from healthy persons as far as possible.

Materials and Methods

The adrenals from 62 autopsies were studied, in 6 cases only one gland could be used as the other had been damaged during dissection, leaving a total of 118 organs for this study. Age and sex-distribution are presented in Table 1. An attempt was made to obtain normal glands, i.e. those from healthy subjects, at least in the group of adolescents 15 years and older and adults. Here a strict selection was done and only those cases of sudden death were used that fulfilled all of the following 3 criteria

1. death within 24 h after injury (details are given in Table 2)
2. no major pathological findings, aside from the injuries, at autopsy
3. heart less than 400 g (to exclude hypertension).

The adrenals were fixed in neutral 5% formalin for at least 24 h. Following careful dissection of remaining fat tissue from the surface, the glands were weighed and then cut completely into slices 3 mm thick perpendicular to the long axis. All of the blocks were embedded in paraffin, 5 μ sections were mounted on square glass slides 5 × 5 cm, stained with H & E and mounted with Eukitt. From these slides drawings were made at 10 × magnification using an ordinary slide projector. The outlines of capsule, medulla, blood vessels, and where present

Table 1. Age and sex distribution

	Male	Female
0–1 month	11	2
1–6 months	4	8
$^1/_2$–2 years	4	4
2–10 years	1	2
10–20 years	9	3
20–40 years	6	3
Above 40 years	3	2
Total	38	24

Table 2. Causes of death in adolescents and adults

Age	Sex	
15	Female	Traffic accident with severe head injury
15	Male	Traffic accident with severe head injury
15	Male	Traffic accident with severe head injury
18	Male	Traumatic rupture of aorta
18	Female	Multiple injuries in traffic accident
18	Male	Severe head injury, laceration of lung
19	Male	Gun shot wound, chest, with injury of aorta
20	Male	Traffic accident with severe head injury
22	Male	Acute intoxication (Heroin?)
23	Male	Gun shot injury, heart
23	Male	Multiple injuries in traffic accident
26	Female	Multiple injuries due to fall from 4th floor
29	Male	Exsanguination from head injury in acute alcohol intoxication
34	Male	Multiple injuries in traffic accident
36	Female	Multiple injuries in traffic accident
40	Female	Traffic accident with severe head injury
43	Female	Exsanguination from laceration of carotid artery
43	Female	Skull fracture with extensive subdural haemorrhage
45	Male	Traffic accident with severe head injury
47	Male	Traffic accident with severe head injury
52	Male	Multiple injuries with laceration of the heart in traffic accident

fetal cortex, were drawn in different colors. The areas occupied by these different structures were measured by means of a manual-optic picture analyser (Kontron MOP-AM 01).

The sum of the areas of each compartment (for example medulla) in all sections of one adrenal is proportional to the volume occupied. There is only a minor difference between the specific weights of medulla and cortex. Hammar (1924) found values between 1.030 and 1.075 for the adrenal cortex and 1.042 to 1.090 for the medulla. The weight can thus easily be calculated from the volume. The shrinkage though occuring during preparation of the sections which is somewhat different for medulla and cortex is not taken into consideration. Since this however is a constant error affecting all the organs studied equally the method employed yields reproducible and comparable results.

The shape of the adrenal medulla at low power magnification can be recognized pretty well by examining the drawings of all sections of each case.

All sections in addition were examined with the microscope.

Results

1. Weight and Volume

The values for weights and volumes – always referring to one gland – are presented in Figs. 1 and 2. The average volume of the adrenal medulla in relation to the volume of the whole organ is 0.36% in infants who died within 1 week after birth. This corrresponds to an average medullary weight of 0.012 g. During the 2nd year of life the average values are 4.2% and 0.08 g, there is a considerable variation of individual values in this group though. The more pronounced increase of the relative volume of the medulla is due to the involution of the fetal cortex and the concomitant decrease

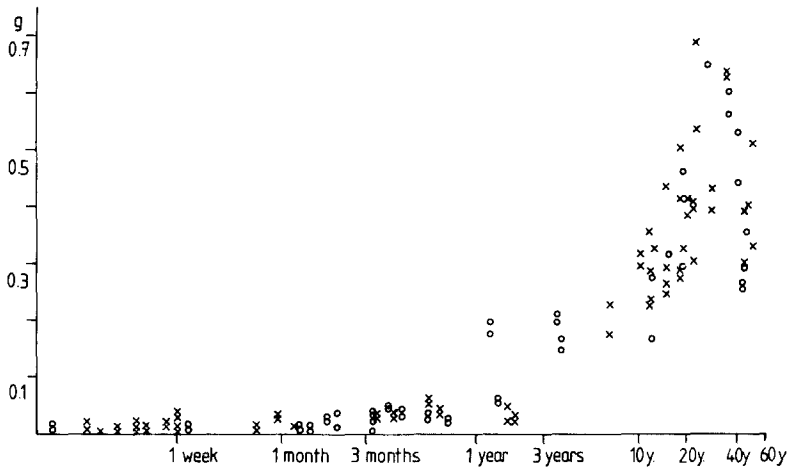

Fig. 1. Adrenal medullary weight in grams. Age drawn in logarithmic scale. x = male; o = female

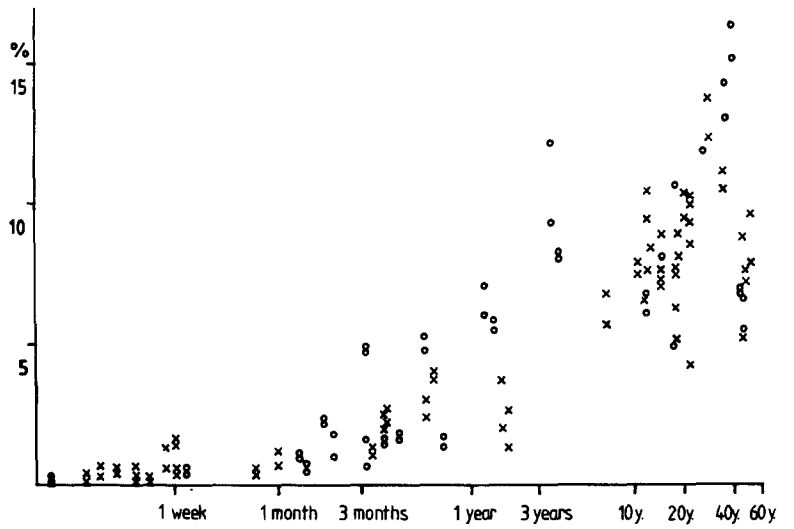

Fig. 2. Amount of adrenal medullary volume in % of total adrenal volume. Age drawn in logarithmic scale. x = male; o = female

in weight of the whole adrenal. Between 10 and 13 years of age, average values of 7% and 0.28 g respectively are found, in the 15 year old 7.8% and 0.32 g, in adults finally 9.0% and 0.43 g. In adults younger than 40 years the values of 9.9% and 0.46 g are clearly higher than in those older than 40 years where we find 7.1% and 0.36 g. The average weight of the adult adrenal gland in both groups is 5.1 g. The weights and volumes in adults grouped according to sex and age are listed in Table 3.

2. Shape of the Adrenal Medulla

In the newborn and during the first days of life, the adrenal medulla is located in the central part of the adrenal as a thin narrow plate, sometimes

Table 3. Average values of weights and volume percentage in various populations of adults

	n	Adrenal weight in g	Volume percentage medulla	Weight adrenal medulla in g
Adults over 18 years	18	5.1	9.0	0.43
Adults 18–40 years	13	5.0	9.9	0.46
Adults over 40 years	5	5.1	7.1	0.36
Men over 18 years	12	5.2	8.6	0.42
Men 18–40 years	9	5.2	8.9	0.43
Men over 40 years	3	5.2	7.6	0.39
Women over 18 years	6	4.7	10.0	0.44
Women 18–40 years	4	4.6	12.2	0.51
Women over 40 years	2	4.9	6.3	0.30

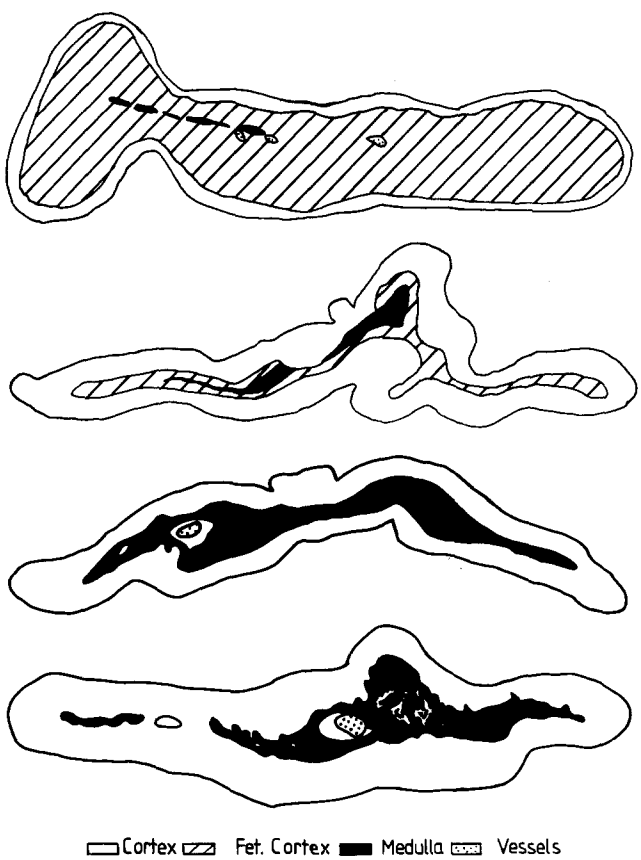

Fig. 3. Shape of the adrenal medulla at various ages. From top to bottom: 1 day, 3 months, 20 years, 47 years. Magnification ca. 4 ×

in several portions, surrounded by fetal cortex. During the ensueing involution of the fetal cortex the adrenal gland developes its characteristic shape with a ridge over the central vein and two flat processes (alae) on both sides, of usually rather unequal size. Already at the age of 2 months the medulla starts to swell, usually in the vicinity of a larger vein. The medullary plate too as a whole becomes thicker and larger, gradually protruding into the alae. At this age a thin layer of connective tissue, the medullary capsule, is formed between cortex and medulla. It is made up of the collapsed fibrous framework emerging during the involution of the fetal cortex. This fibrous capsule in turn soon dissolves and has largely disappeared at the age of 3 years. The medulla now is indented by the central vein. The central vein is at first attached to the dorso-caudal surface of the adrenal, it then penetrates the gland obliquely, for a short distance surrounded by a cuff of cortical tissue, the "central cortex", and finally enters the medulla. Depending on the plane of section we will therefore find either cortical tissue, medulla or both of these around the central vein. In young adults, the medulla is found extending over approximately $^3/_4$ of the length of the adrenal, it approaches the medial extremity of the organ whereas in sections from the lateral end no medullary tissue is usually found. The medulla forms a bulge adjacent to or surrounding the central vein, from this bulge a plate of medullary tissue extends on both sides into the alae. The border between medulla and cortex around the bulge and at the surface of the plates originally is even. At the edges of the plates it appears ragged with strands of medullary tissue extending into the cortex. Beginning at about the 12th year of life, the medullary-cortical border gets increasingly irregular and ragged. This process starts around the central vein where in the course of time interdigitation of medullary and cortical tissue occurs. This eventually leads to the formation of islands of cortical tissue in the medulla and vice versa. This "intermingling" attains a larger degree after the age of about 30 years. It appears most pronounced in the thick portion of the medulla around the central vein. Irregularities also appear at the corticomedullary junction of the flat medullary processes within the alae. Commonly after the 40th year of life here too islets of cortical tissue are found within the medulla.

3. Histology

In the newborn and very young infants the medulla is made up of medulloblasts lying in loosely arranged rosette formations. At about the 2nd month of life complexes of characteristic medullary cells appear, their number rapidly increases, at the same time the immature cells disappear. At about 4 months only a few rosettes of medulloblasts are encountered. In all age groups, starting with the newborn, ganglion cells are found within the medulla. Their number is small as a rule, occasionally they form small groups, now and then around nerves. In almost all adrenals of adults, sometimes also in those of infants and children, small aggregates of lymphoid cell elements are present in the medulla.

Discussion

The adrenal gland of the newborn is made up of 3 types of parenchyma, each subject to a different postnatal development:

1. The fetal cortex constituting with over 70% the major portion of the glandular volume (Tähkä 1951). During pregnancy it produces certain steroids that reach the placenta via the umbilical cord. In the placenta they are transformed into oestrogen which in turn enters the maternal circulation. After birth this process naturally ceases and rapid involution of the fetal cortex, now no longer necessary, takes place.

2. The adult cortex surrounding the fetal cortex the volume of which accounts for approximately 20% of the adrenal gland in the newborn. It produces the mineralo- und glucocorticoids required by the organism. At birth it is made up of merely 2 layers – zona fasciculata and zona glomerulosa. The third layer, zona reticularis, is formed during early childhood. The changes seen during the process of involution of the fetal cortex and the transformation taking place in the permanent cortex during infancy and childhood have been described in detail by several authors (Rotter 1949; Dom 1973).

3. The adrenal medulla which at birth constitutes less than 1% of the total volume of the gland. It is made up of immature cells. Early in the first months of life they are replaced by mature medullary cells. No unequivocal age-dependent alteration of these cells is recognizable later on. (This statement refers of course only to the picture at it is seen in H & E stained paraffin sections. Differences might be discovered by employing special stains and histochemical reactions on surgical material.) Alterations in the shape of the adrenal medulla as a whole are evident at low-power magnification. With increasing age, more pronounced after about 30 years, the cortical-medullary border becomes irregular, islets of cortical tissue are found within the medulla and vice versa groups of medullary cells within the cortex. This process is similar to what has been described for the ageing of the adrenal cortex where only in young adults is the "text-book picture" of a regular stratification with parallel borders between glomerulosa, fasciculata and reticularis found. With advancing age an increasing interdigitation between zona fasciculata and reticularis takes place and the zona glomerulosa no longer forms a continuous subcapsular layer (Kreiner and Dhom 1979). In infancy, the adrenal medulla shows a rapid growth in regard to absolute weight as well as volume in relation to the whole gland, later in childhood the rate of growth diminishes, in adolescents of 15 years the average values are still somewhat below those of adults. The relative medullary volumes found by Swinyard (1943) in 10 subjects between 0 and 17 years of age are within the range of those obtained in the present study. The weights are not stated in this paper of Swinyard (1943). Table 4 presents the figures for the weights of the adult human adrenal medulla as they were given by various authors. It appears, that the weight for one gland is around 0.4 g on the average, with deviations of some 0.2 g above and below. No great differences are encountered between the values of different

Table 4. Average weight of the adrenal medulla in adults

	n	Number of adrenals examined	Weight adrenal medulla	Minimum	Maximum
Hammar (1924)	8	10	0.37	0.156	0.652
Quinan and Berger (1933)	50	100	0.44	0.20	0.67
Swinyard (1940)	15	26	0.40	0.21	0.65
Liebegott (1952)	5	5	0.48	not stated	
De Lellis et al. (1976)	6	10	0.47	not stated	
Rudy et al. (1980)	4	6	0.39	0.29	0.53
Own investigations	18	34	0.43	0.26	0.70

authors. It seems particularly noteworthy, that the figures of Quinan and Berger (1933) who weighed the dissected medullary tissue directly, agree well with those of the other studies where morphometric methods were employed. A sex-difference in adrenal medullary weight is not apparent in the present investigation. For the whole adrenal gland (and thus also for the adrenal cortex which in adults makes up some 90% of the organ) a lower average weight in females was found by several authors (Rössle and Roulet 1932; Sasano et al. 1956; Kreiner and Dhom 1979). That no sex-difference in medullary weight is evident might perhaps be due to the fact, that only comparatively few women were entered into this study. Swinyard (1940) found a lower average weight of the female adrenal medulla. In the paper of Quinan and Berger (1933) the weights are listed without information as to age and sex. In the other publications listed in Table 4, the number of cases is too small to assess this point. It is also not possible to say, whether – as it is known for the adrenal cortex – the average medullary weight of an unselected autopsy population is higher than that of cases of sudden death. Firstly, there is both in this study and in those of other authors, a remarkable deviation of individual values, and secondly, in some papers the cause of death is not stated.

In spite of these limitations, the values found in this population of healthy persons who had died suddenly can serve as a baseline for evaluation of a possible adrenal medullary hyperplasia. Such a diffuse growth of the adrenal medulla can be demonstrated unequivocally only after determination of the medullary weight, either by weighing the dissected medulla directly or by means of morphometric methods. Examining a few sections of surgically removed adrenals (Schwab and Denninger 1952; Montalbano et al. 1962) can give a false impression of medullary hyperplasia due to the uneven distribution of the medulla within the organ. A decrease in size of the adrenal cortex will also lead to a shift in the cortico-medullary relation towards the medulla and thereby create the appearance of medullary hyperplasia. The shape of the medulla cannot be used as an indicator of adrenal medullary hyperplasia. There are, as can be seen in this population of healthy subjects, considerable individual variations. Medullary tissue is

always found in the alae, this therefore is not an indication of medullary hyperplasia.

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