

Focal Adrenalitis

Its Frequency and Correlation with Similar Lesions in the Thyroid and Kidney

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Summary. A retrospective survey of focal adrenalitis, in autopsy material, was performed. A total percentage of 48% of cases showed signs of focal adrenalitis, 12.5% of them of 2 + degree. This maximal degree of adrenalitis was found more frequently in older persons, of both sexes. Half of the patients, with this maximal degree of adrenalitis, had abdominal pathology, mainly inflammatory processes. In comparison with similar inflammatory foci in the kidney a good correlation was found between the degree of focal adrenalitis and that of focal interstitial nephritis. An infectious pathway, propagated from the neighboring organs, can be taken in consideration, as the etiology of focal adrenalitis, despite the good parallelism found in the frequency and degree of focal adrenalitis and similar lesions in the thyroid too, believed to be of an immunologic character.

In the classical book on pathology, entitled: "Pathologische Anatomie" edited by Ludwig Aschoff, in 1919 (5th edition) and in 1923 (6th edition), the term Hypernephritis was applied to inflammatory conditions of the adrenals (Aschoff, 1919, 1923). In the textbooks of pathology of contemporary editions this term was dropped, however, the inflammatory conditions of the adrenal were mentioned briefly (Sommers, 1971). In all these books the rarity of adrenalitis case was stressed. S. C. Sommers (1971), in the textbook edited by Anderson, explained this rarity as due to the antiphlogistic effects of the corticosteroids produced by the gland.

The finding of small foci of lymphocytes and plasma cells in the adrenals, mainly in perivenous position, called focal adrenalitis, was considered by Sommers (1971) not as an intrinsic adrenal disease, but as a pathology accompanying retroperitoneal chronic phlebitic conditions, mainly chronic pyelonephritis. Foci, composed of similar cells, in other organs, mainly thyroid and kidney can be seen in diseases considered as of immunologic etiology (Witebsky, Rose, Terplan, Paine, and Egan, 1957).

A survey of 168 autopsies was undertaken to define the frequency of such focal adrenalitis, its rate of appearance with other diseases and its relationship, in frequency and degree, to similar cellular focal infiltrates in the thyroid and kidney.

Material and Methods

The microscopic slides containing the adrenals, thyroid and kidney of 168 autopsies performed in the whole year of 1970 in the Department of Pathology, Meir Hospital, were re-examined. A whole year was chosen to exclude seasonal differences. In most of the cases both adrenals, both lobes of the thyroid and both kidneys were represented. If the adrenals

were not taken for microscopic examination, the case was disregarded. If one of the other two organs lacked, the case was accepted and assessed. In most of the slides with adrenals, both parts, cortex and medulla, were included, because the material taken routinely for microscopic examination was from the middle of the organ.

The slides were stained with hematoxylin-eosine stain. In some cases Giemsa stain and/or Van Gieson's stain were used too.

The cases with the following pathologic conditions were excluded from the survey: leukemias, lymphomas, amyloidosis, primary glomerular diseases, severe vascular nephropathies, congenital kidney malformations, metastases to the adrenals and adrenal hemorrhages. After this eliminations a total of 135 cases remained and were examined. Reducing the patients died in the first decade of life, 112 adult acceptable cases remained.

Focal adrenalitis was defined by the finding of small or larger foci of round cell aggregates between cortical cells or around blood vessels, mainly veins or venules. Small round cells in the medulla were not considered as such, as they could not be differentiated from normal medulla cells. The cells accepted as signs of focal adrenalitis were of lymphocytic or plasmacytoid type, with few larger round cells in some of the cases. If the type of the cells was doubtful and extramedullary hematopoiesis was suspected, Giemsa stain was applied and the finding compared with hematopoietic cells in other organs, mainly liver and spleen, in cases of myeloid metaplasia. No lymph follicles were seen in the areas of this kind of infiltration. No necrosis or granulocytes were seen in these foci, but some atrophic or degenerated adrenal cells could be seen. In the foci or around them, congestion could be detected. Most of the foci were in the cortico-medullary region. No adrenal capsule thickening, periadrenal fibrosis or inflammation were seen in the focal adrenalitis cases. The number and extent of the foci was assessed semiquantitatively as 0 if absent or of \pm to 2+ degree, depending on the size and number of the foci (Figs. 1-3).

In the kidneys, foci of lymphocytes or round cell aggregates were looked upon in interstitial or perivascular position. Cellular infiltrations in atrophic or fibrotic subcapsular regions were not considered. If hydronephrosis or signs of pelvic inflammation were seen the case was considered as pyelonephritis. The foci were assessed semiquantitatively as of \pm to 3+ degree depending on their number and size.

The number of lymphocytic or mononuclear cell aggregates in between the thyroid acini were assessed similarly to the other 2 organs described above. In and around adenomas, in fibrotic areas or around calcified areas such infiltrations were not considered compatible for assessment.

In paired organs the assessment of the degree of involvement of the lesions was the average one, despite the difference in some cases in the degree and even in the presence or absence of the lesion between the two parts of the paired organs.

Results

The total number of autopsied cases acceptable for this study was 135. Sixty of them were females and seventy-five males. The total number of focal adrenalitis cases (F.A.) was 65 (48%), thirty-five of them females and thirty males. 17 cases (12.5%) had 2+ degree of F.A., 31 cases (23%) 1+ degree and 17 cases (12.5%) \pm degree of F.A. No sexual preponderance of the lesion was seen even if analysed by degree of the lesion: 2+ degree of F.A. was seen in 8 females and in 9 males, 1+ degree was seen in 20 females and 17 males, \pm degree was observed in 7 females and 10 males. No 3+ degree of F.A. was seen in the studied material. The cases with 2+ degree of F.A. were considered as the significant ones and all the statistical comparisons as to the frequency of the lesion, rate of appearance with other diseases or with similar lesions in other organs, were calculated and compared with this group of 17 cases of 2+ degree F.A.

The F.A. cases were divided in decades of years of the patients, as seen in Fig. 4. No F.A. cases were seen among the 13 cases died in the first decade of

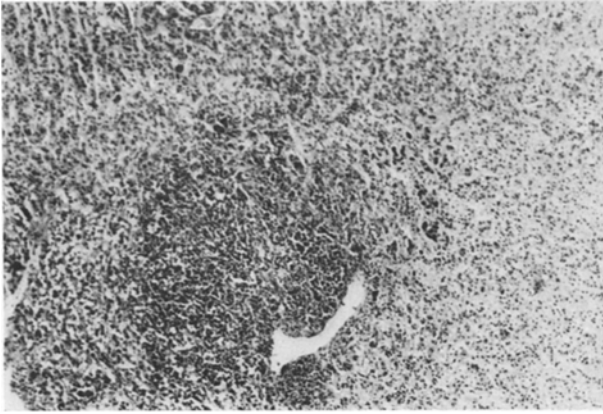


Fig. 3. 2+ degree of focal adrenalitis.
H.E. $\times 40$

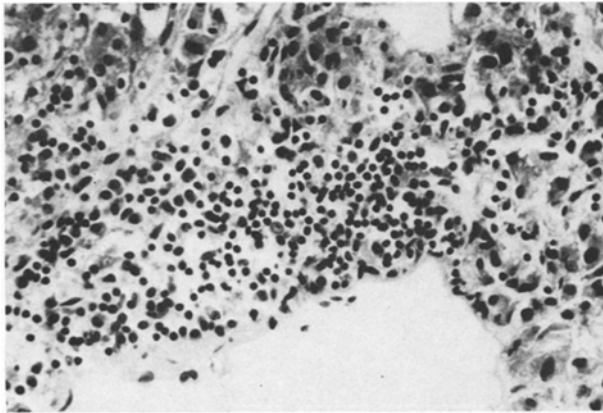


Fig. 2. 1+ degree of focal adrenalitis.
H.E. $\times 100$

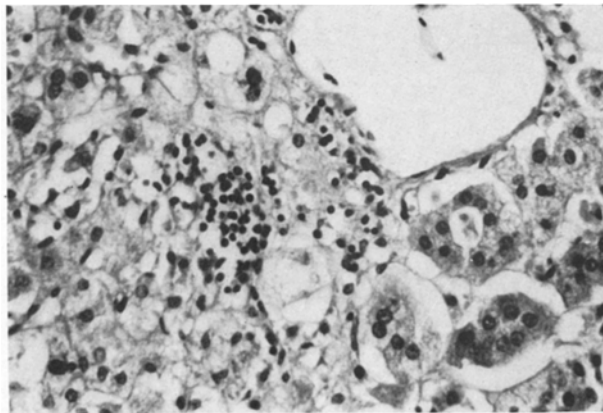
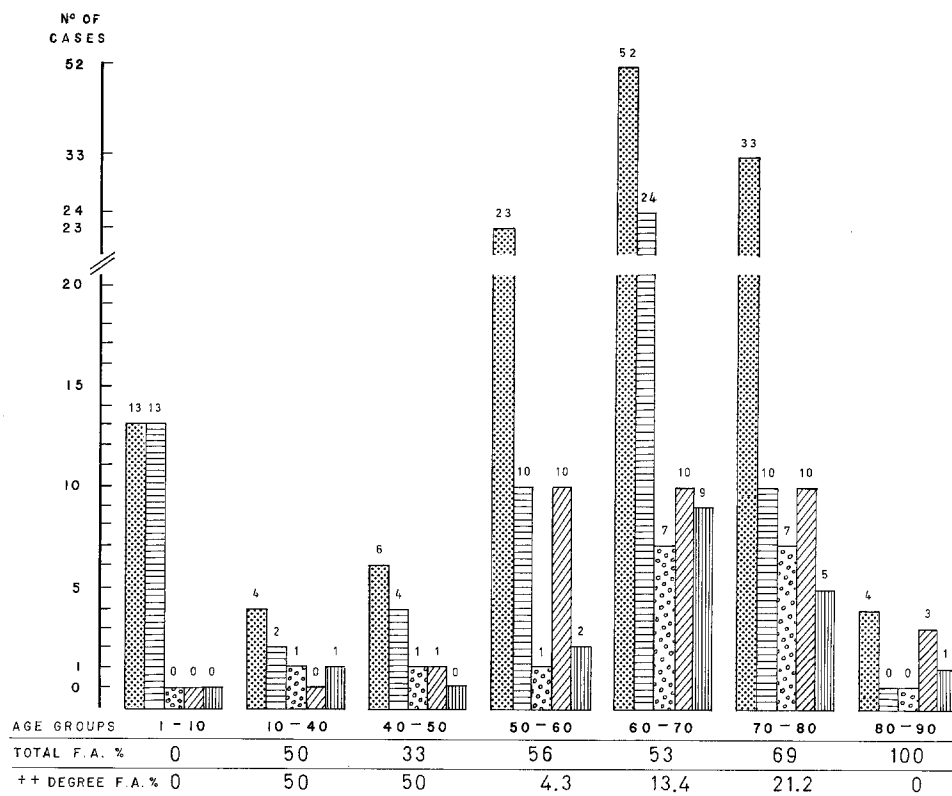


Fig. 1. \pm degree of focal adrenalitis. H.E.
 $\times 100$

their life (most of these cases were new-born babies). The decades between the age of 10 and 50 years could not be considered statistically, as only 4 or 6 autopsies have been found, but even in this period sporadic cases of F.A. were seen. 56% of the total autopsied cases, which died in the 5th decade of their



- TOTAL NUMBER OF ADRENALS
- ▨ NUMBER OF NORMAL ADRENALS
- NUMBER OF ++ DEGREE F.A.
- ▧ " " + DEGREE F.A.
- ▩ " " ± DEGREE F.A.

Fig. 4

life, had some degree of F.A. The percentage of $2+$ degree of F.A. in this period was 4.3%. In the 6th decade the total percentage of F.A. cases was quite the same as in the prior decade: 53%, but the percentage of $2+$ degree F.A. raised to 13.4%. In the 7th decade this percentage raised to 21.2% and the total percentage of F.A. cases raised to 69%. The percentage of F.A. in the 8th and 9th decades could not be calculated, as only 4 autopsies were performed on persons in this age range.

No seasonal preponderance of the lesion was seen, as 1 or 2 cases of $2+$ degree F.A. were found in each month of the year.

The main anatomopathologic findings in the 17 cases with $2+$ degree F.A. can be seen in Table 1. 8 cases (47%) had abdominal pathology. 3 of these

Table 1

17 cases of 2 + degree F.A.		Cases without F.A.
Abdominal pathology	8 (47 %)	20 %
Heart failure	5 (29 %)	35.5 %
Encephalomalacia	2 (11.7 %)	20 %
Pulm. pathology	2 (11.7 %)	24.5 %)

Table 2^a

Total pathology	Adrenal		Thyroid		Kidney	
	65	58 %	8	14 %	69	61 %
2 +	17	26 %	6	75 %	28	41 %
1 +	31	48 %	1	12.5 %	34	48 %
±	17	26 %	1	12.5 %	7	11 %
0	47	42 %	48	86 %	43	39 %

^a Calculated on 112 adult autopsied cases.

8 cases had gastric or duodenal ulcers, one of them perforated, four other cases out of the eight had abdominal malignancy, one of them a perforated colon carcinoma and peritonitis. The 8th case had a severe staphylococcal enterocolitis. 5 cases (29 %) with 2 + degree of F.A. had myocard infarets and heart failure as the main pathologic finding, 2 cases (11.7 %) died because of encephalomalacia and other 2 (11.7 %) had pulmonary pathology: one with massive pulmonary embolism and the second one: chronic pulmonary disease with cor pulmonale.

In comparison, the 70 cases without F.A. had a lower rate of abdominal pathology and a higher or the same rate of the other similar pathologies (see Table 1).

The total percentage of the thyroid lymphocytic focal infiltration was 14 %, the interstitial kidney infiltration with the same kind of cells was 61 %. The total percentage of F.A. cases was 58 % (the 13 cases in the age period of 0-10 years were not included in all these calculations) (see Table 2).

In the thyroid most of the lesions were of 2 + degree (75 %). In contrary, in the adrenal and kidney most of the lesions were of 1 + degree (48 %) (see Table 2)

The percentage of the 2 + degree pathology in the thyroid and kidneys were compared in each group of patients with 2 + degree F.A. and normal adrenals, the following results were obtained (see Table 3). In the 17 cases with 2 + degree F.A. 20 % of the thyroids showed lymphocytic infiltrates, all of them of 2 + degree and 59 % of the kidneys had interstitial infiltrations (70 % of them of 2 + degree). In contrary in the 47 cases with normal adrenals, 6.2 % of the thyroids and 58 % of the kidneys were pathologic which is a very similar percentage to that of the pathologic kidneys in the whole F.A. group (61 %).

Table 3^a

Adrenal		Thyroid			Kidney		
No.	Degree	No.	%	% 2 +	No.	%	% 2 +
17	2 +	10/2	20	100	17/10	59	70
-1	1 +	20/4	20	75	31/20	64	45
17	±	7/0	0	0	17/10	58	33
47	0	32/2	6.2	50	47/28	58	21

^a Calculated on 112 adult autopsied cases.

A good correlation was found between the degree of the F.A. and the percentage of the 2+ degree lesions in the other organs: 2+ degree of lesions were found low in other organs of the ± group of F.A. (0 for thyroid and 33% for the kidney) and proportionally higher percentage in the 1+ or 2+ groups of F.A., 75—100% for the thyroid and 45—70% for the kidney (see Table 3).

Two cases were found in which all 3 organs (adrenal, thyroid and kidney) showed 2+ degree of lymphocytic infiltrations.

Discussion

The only similar report, in the medical literature, on the prevalence of focal adrenalitis in autopsy material, in the last 15 years, was that of Petri and Nerup (1971). In their survey of 657 autopsies they found a total of 30 cases of F.A. (18.6%). In our survey the total percentage of F.A. was 48% including all age groups. The discrepancy between the two surveys can be explained by the difference in the method of semiquantitative assessment. It can be that cases assessed as ± degree of F.A. in our survey and even the 1+ degree of F.A. would have been assessed as normal by Petri and Nerup (1971). 2+ degree of F.A. in our material was found in 12.5% which is nearer to the total percentage of 18.6% of cases in Petri and Nerup's survey (1971). The fact that in Petri and Nerup's survey 3.4% of cases were of 3+ degree and we have not assessed cases of such degree of involvement at all, substantiates the disuniformity in the method and temperament of assessment in the two surveys. The other possibility of this disagreement in the percentage of F.A. cases can be, that due to unknown causes, the prevalence of F.A. is higher in our country or hospital, than in Denmark, where the work of Petri and Nerup was performed. A difference in the prevalence of focal thyroiditis, was reported as occurring between English and African studies (Pulvertaft, 1969).

In the forementioned survey (Petri and Nerup, 1971) 4 out of the 13 patients with 3+ degree of F.A. had diabetes mellitus, in contrary in our survey only 2 out of 17 patients with 2+ degree of F.A. had diabetes. The same two patients in our survey had 2+ degree of focal thyroiditis too. They belong to the 5 cases with 2+ and 1+ degree of thyroiditis, which had 2+ degree (2 cases) and 1+ degree (3 cases) of F.A. and can be considered as subclinical Schmidt's syndrome (Carpenter, Solomon, Silverberg, Bledsoe, Northcutt, Klinenberg, Bennett, and McGehee, 1964). The clinical picture of all these 5 cases was variable

and no clinical evidence of thyroid or adrenal insufficiency was noted. The higher rate of diabetes in Addison's disease is known (Selby, 1962).

In both surveys, that of Petri and Nerup (1971) and ours, no difference was found in the prevalence of F.A. in one of the sexes. In contrary, focal thyroiditis is more prone to be found in females (Harris, Summerell, and Swan, 1973).

The prevalence of F.A. in different decades of ages was difficult to assess, because no uniform number of autopsies have been examined in each decade period. In contrary to our findings, which indicated an increase with age of the frequency and degree of F.A., no such tendency was found in Petri and Nerup's survey (1971). It is known that the incidence of autoantibodies increases steadily with age up to around 60-70 years (Roitt, 1973).

Similar histopathologic picture to that found in F.A. in humans can be achieved experimentally in autoimmune adrenalitis in rats (Andrada, Skelton, Andrada, Milgrom, and Witebsky, 1968), rabbits and guinea pigs (Witebsky and Milgrom, 1962). Female rats are much more sensible to this experimental autoimmune adrenalitis. As no serologic or other investigations to detect adrenal autoimmunity in our patients were performed, we compared the incidence of F.A. to some similar histopathologic findings in other organs, which are considered as having an autoimmune etiology. We were aware to the fact that morphologic similarity does not permit conclusion as to a common etiology and autoimmune inflammation of one organ is not a sign of similar etiologic pathways in other organs. Focal thyroiditis was chosen as the condition for comparison.

Focal thyroiditis is accepted in human patients and experimentally as an autoimmune condition (Williams and Doniach, 1962). The prevalence of focal thyroiditis in autopsy material varies between 10% (Roitt, 1973), to 56% (Kenedy, 1970). The total percentage of focal thyroiditis in our survey was 14%. 75% of them were of 2+ degree. Interestingly the only 2 cases of focal thyroiditis which were found in the 10 cases of the 2+ degree F.A. group were of 2+ degree too, but 3 cases, which consisted 75% of 1+ degree F.A., showed 2+ degree of thyroiditis too. In the group of patients with normal adrenals 6.2% of focal thyroiditis was found, however, only one of 2+ degree. It can be concluded that focal thyroiditis in our survey was found significantly more in the cases with focal adrenalitis and less in the cases with normal adrenals and a quite good correlation between the degrees of the lesions can be seen too.

To deny or confirm Sommer's assumption (1971) of a connection between kidney infiltrations and F.A. their frequency and degree of severity were compared.

Focal interstitial nephritis can be a histologic component of pyelonephritis, but experimentally similar findings were achieved by injections of autologous kidney extract (Sugisaki, Klassen, Milgrom, Andress, and McCluskey, 1973) and appears in classical autoimmune diseases. The overall percentage of this kind of lesion in our survey was 61%. In the group of patients with normal adrenals 58% of the kidneys showed interstitial nephritis. In the group with 2+ degree F.A. 70% of them had 2+ degree of focal nephritis, in the group of patients with normal adrenals only 21% of 2+ degree of focal nephritis was found, therefore it can be concluded that the interstitial focal nephritis in our survey

showed a good correlation in the degree of the lesions with that of F.A., but not in the frequency of the lesions.

The clinical significance of focal adrenalitis cannot be discussed. The survey was based on a retrospective autopsy material, therefore no clinical or laboratory investigations were performed concerning the adrenal functions.

In conclusion, despite the restrictions of retrospective studies it can be concluded that F.A. can be found more in older age group patients, with inflammatory processes in abdominal region, it correlates with the degree of similar lesions in the kidney, however, a good correlation was found with the frequency and degree of focal thyroiditis too.

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