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Renal involvement in sarcoidosis

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Summary

Among 152 sarcoidosis patients, 11% had hypercalcaemia, 62% had hypercalciuria and 13·8% had at least one renal stone. Impairment of renal function was mostly conspicuous in patients with hypercalcaemia. Twenty-five successful percutaneous renal biopsies were performed. Epithelioid granulomas were seen in ten cases, with inflammatory reaction more prominent than in other organs involved by sarcoidosis, due to simultaneous pyelonephritis. Thickening and hyalinization of capsular membrane and glomeruli as well as arterial walls were frequently encountered. Amyloid deposits could be seen in one case with chronic lung infection. Histopathological changes specific of sarcoidosis are related to an abnormal amount of serum gammaglobulins and calciuria exceeding 200 mg in 24 hr, which seem to be the best tests of involvement by the disease.

Tubular reabsorption of calcium was low in two patients with hypercalciuria, which was corrected after corticosteroid treatment.

High intestinal calcium absorption was lowered after hydrochlorothiazide had decreased urine calcium.

Sarcoidosis patients with renal involvement can be roughly divided into two groups (Löfgren, Snellman & Lindgren, 1957), according to the degree of their calcemia.

The cases with hypercalcaemia usually have an impairment of renal function, and those with granulomatous renal lesions but normal calcaemia have a well preserved renal function; however, some cases of granulomatous sarcoid nephritis are reported with mainly tubular (Ogilvie, Kay & Moore, 1964) and sometimes glomerular (Coburn *et al.*, 1967) dysfunction in spite of normocalcaemia.

The specific renal localizations were first described by Chanial (1937), and Spencer & Warren (1938). The frequency of renal sarcoid lesions in autopsy material has been rated at 27% by Vogt (1949), 20% by Ricker & Clark (1949), 13% by Longcope & Freiman (1937) and 7% by Branson & Park (1954). Löfgren *et al.* (1957) have performed a renal biopsy in sixteen patients with sarcoidosis and found four cases of epithelioid granulomas.

But besides those specific lesions, many cases are described with renal insufficiency and histopathological changes not necessarily connected with sarcoidosis. It seems however that a chronic pyelonephritis is frequently encountered (Sorger & Taylor, 1961); moreover, Teilum (1948) described hyaline changes in the glomeruli and the arterial walls, similar to those seen in hypersensitivity diseases, even resembling amyloid deposits.

Material and methods

152 cases of sarcoidosis with histological confirmation represent the material used in the present study.

All cases had at least one determination of blood calcium, a complete urine analysis and a plain radiography of lumbar region performed.

Various renal function tests were carried out in most cases; fifty-eight among them had at least a measurement made of endogenous creatinine clearance, 15 min PSP excretion, maximal concentrating ability or osmolality, and 24 hr calciuria and titrable acidity; the daily intake of calcium was reduced to about 250 mg before the latter test was carried out. In thirty-five cases, a percutaneous renal biopsy was performed.

In two patients, citrate was assessed in blood and urine, and tubular reabsorption of calcium was computed, the level of diffusible calcium being taken into account; the measurements were made before and after 20 days of treatment with cortisone, 150 mg/day.

In two other patients with high calciuria but normal blood calcium, intestinal absorption of ^{47}Ca was studied according to the technique described by Avioli *et al.* (1965) with a daily intake of roughly 500 mg of calcium; a dose of 10μC of ^{47}Ca was given, and blood isotope activity was assessed at various times during 4 hr; then hydrochlorothiazide was administered for 10 days 100 mg/day, during which calciuria was estimated each day; on the tenth day of treatment, another test with ^{47}Ca was carried out.

Results

Blood calcium was found higher than 11 mg/100ml in seventeen cases (11%). 24 hr calciuria exceeded 200 mg in thirty-six of the fifty-eight cases where it was studied (62%).

The results of urine analysis are recorded in Table 1.

TABLE 1. Urine analysis in 152 cases of sarcoidosis

	Number of cases	%
Proteinuria	55	36
Abnormal urine sediment	20	13
haematuria with lithiasis	10	
without lithiasis	4	
casts (hyaline, leucocytes, granular)	9	

There was abnormal proteinuria in 36% of the cases and significant elements in the sediment in 13%.

Twenty-one patients had at least one renal stone; one among them had a multiple, bilateral, lithiasis. There was a marked tendency to lithiasis in patients with hypercalcaemia (nine out of seventeen cases) or hypercalciuria (fifteen out of thirty cases) (Table 2).

Renal function tests were impaired in most cases with hypercalcaemia. There is some overlap in the results recorded in Table 3; while the mean endogenous creatinine clearance was 71 ml/min in the patients with hypercalcaemia, two among them had much lower values: 28 ml and 31 ml; the 15 min PSP excretion was 8 and 14% respectively in the same patients; these were also the only cases where the diastolic blood pressure reached 120 mmHg.

The thirty-five percutaneous renal biopsies were successful in twenty-five cases (Table 4).

TABLE 4. Histopathological changes in twenty-five successful needle biopsies

	Cases
Epithelioid granulomas	10
Hyaline deposits (capsules, glomeruli, arterial walls)	9
Interstitial inflammation	8
Glomerular hypercellularity	4
Interstitial fibrosis	2
Pericapsular fibrosis; adhesions	2
Amyloid	1

Histopathologically, there were epithelioid granulomas to be found in ten cases, scattered in the cortex or the medulla, with an inflammatory reaction more prominent than in other organs involved by sarcoidosis, due to the simultaneous occurrence of pyelonephritis; the epithelioid nodules are not easily distinguished from the surrounding tissue, their limits being imprecise; the second modification, by frequency of incidence, was thickening and hyalinization of capsular membrane, hyalinization of some glomeruli and sometimes arteriolar walls. In one instance amyloid deposit could be

TABLE 2. Twenty-one cases of renal lithiasis in 152 patients with sarcoidosis

		Number of cases	Patients tested	With lithiasis
Blood calcium	$\geqslant$ 11 mg/100 ml	17	152	9
Blood calcium	$<$ 11 mg/100 ml	135	152	12
24-hr urine calcium	$>$ 200 mg	36	58	15
24-hr urine calcium	$<$ 200 mg	22	58	6

TABLE 3. Renal function tests in fifty-eight cases

Blood calcium (mg/100 ml)	Creatinine clearance (ml/min)		15 min PSP (%)		Max. urine conc. and osmolality		Titrable acidity (mEq/24 hr)	
	mean	range	mean	range	mean	range	mean	range
>11 mg	71	28–127	20	8–42	mOsm. 383 Conc. 1011	288–792 1010–1030	12	3–30
<11 mg	101	69–177	32	24–51	mOsm. 788 Conc. 1023	358–1240 1014–1030	23	16–48

seen in the arterial walls; this patient had a marked lung involvement with fibrous transformation, bronchiectasis and chronic infection. Hypercellularity of the glomeruli, pericapsular or interstitial fibrosis were less frequently encountered.

The results of calcium and citrate handling by the kidney in two patients are seen in Table 5. The two patients studied with ^{47}Ca, had an increased absorption of the isotope; after the treatment with hydrochlorothiazide, their calciuria was reduced by more than 50%; the absorption of ^{47}Ca was equally much lower (Table 6).

Comments

The incidence of tuberculoid granulomas in the twenty-five kidney biopsies was as high as 40%, a number higher than that reported by Vogt (1949); Branson & Park (1954) found only 7% of granulomas in their cases, but they studied necropsies of chronic cases, while all our patients had subacute forms of the disease, usually with elevated gammaglobulins. It appears from this study (Table 7) that hypercalciuria or hypergammaglobulinaemia are good tests for predicting the presence of kidney granulomas.

If hypercalciuria is induced by the presence of granulomas in renal tissue, it would mean that calcium excretion by the kidney could be the cause of increased intestinal absorption of calcium, in accordance with the views of Jackson & Dancaster (1959).

In accordance with Löfgren's statement, the cases with hypercalcaemia had more serious impairment of renal function (Table 3) involving the glomerular filtration rate as well as the tubular tests: however tubular function was more depressed; moreover histopathological evidence of inflammation between the tubules as well as fibrosis were mostly conspicuous in the same cases. The decrease of glomerular filtration rate is related in part to hyaline material present in the glomeruli and the arterial walls, on the other hand, hypercalcaemia *per se* depresses glomerular function.

The incidence of amyloid deposit was low (one case) and is related to a superimposed chronic pulmonary infection: amyloid must not be regarded as a feature of sarcoid tissue.

TABLE 5

	Blood calcium (mg/100 ml)	Plasma water calcium (mg/100 ml)	Blood citrate (mg/100 ml)	GFR (ml/min)	Calcium clearance (ml/min)	Urine citrate (mg/24 hr)	Urine calcium (mg/24 hr)	Tubular reabsorption calcium (%)
(1)	13·4	8·0	5·2	62	4·2	834	520	93·3
(2)	10·4	6·6	2·1	88	2·0	126	194	97·8
(1)	12·8	7·2	3·8	52	4·1	917	432	92·2
(2)	9·8	6·4	2·0	126	4·4	254	414	96·5

(1) before (2) after cortisone, 3 weeks.

TABLE 6. Results of treatment with 100 mg hydrochlorothiazide for 10 days

	Before treatment		Tenth day of treatment	
	Blood ^{47}Ca, 1 hr (% per litre)	24 hr Calciuria (mg)	Blood ^{47}Ca, 1 hr (% per litre)	24 hr Calciuria (mg)
B.H.	2·88	524	1·72	226
R.L.	3·30	481	1·34	207

TABLE 7. Incidence of epithelioid granulomas in twenty-five renal biopsies

		Number of cases epithelioid granulomas present in
16 cases with gammaglobulins	> 1·75 g/100 ml	62·5%
9 cases with blood calcium	> 11 mg/100 ml	33·0%
18 cases with 24 hr calciuria	> 200 mg/100 ml	55·5%
3 cases with creatinine clearance	< 60 ml/min	33·0%
11 cases with 1 hr ESR	> 12 mm	36·3%

Thickening of capsular membrane as well as some degree of hyalinization of the glomerular tuft and the arteriolar walls was a prominent feature in many cases, according to the views of Teilum (1948), who compares these lesions to those seen in 'collagen diseases'.

Renal lithiasis (Table 2) common in cases of hypercalcaemia, had an overall incidence of 13·8% among our sarcoidosis patients which is ten times higher than the number found in a general population by Boyce & King (1959).

Two cases of severe hypertension were encountered and correlated with severest histopathological glomerular lesions. This low incidence of hypertension in patients with sarcoidosis is in agreement with the views of Keech (1951).

The impairment of urine concentration is seen in cases of high urine calcium even with normal calcemia; it is independent of structural changes in the kidney, and disappears rapidly with improvement of sarcoidosis and hypercalciuria.

We studied the renal handling of calcium in two patients with hypercalcaemia and hypercalciuria (Table 5). In each case blood and urine citrate was elevated; glomerular filtration rate was low which could be ascribed to high blood calcium; in spite of a low filtered load of calcium, calciuria was high due to a reduced tubular reabsorption of calcium; a reduction of 1% is sufficient to give a substantial increase of urine calcium.

High levels of citrate in blood and urine are related to those of calcium (Hodgkinson, 1963), and have probably no diagnostic significance; however, low tubular reabsorption of calcium might be ascribed to high citraturia complexing calcium and preventing its tubular transfer (Rose, 1959).

After treatment with cortisone for 20 days all these abnormalities were corrected except for persistent high calciuria in the second patient, which might be explained by some small lowering of tubular reabsorption.

The isotopic study was carried out according to the simplified technique described by Avioli *et al.* (1965); as shown by these authors, good correlation exists between early plasma levels of ^{47}Ca and the actual percent absorption determined by more elaborate methods; this test is not valid unless the intake of calcium is kept constant throughout the study. The values were high in our patients. After hydrochlorothiazide, we noted the well-known reduction in urine calcium (Higgins *et al.*, 1964); on the tenth day of treatment, the absorption of ^{47}Ca was considerably reduced, this might be due to a specific action of the thiazide upon intestinal calcium absorption (Seitz & Jaworski, 1964) or it might reflect the reduction of absorption due to the reduced level of urine calcium; this consideration might give one more argument for the primary action of hypercalciuria on intestinal absorption.

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