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Unilateral "Oligoméganéphronie" with Agenesis of the Contralateral Kidney, Studied by Microdissection

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Summary. The clinical, laboratory and anatomo-pathological observations of a case of unilateral congenital oligonephronic renal hypoplasia with hypertrophy of the nephrons studied by light microscopy and microdissection are reported. The glomeruli were found to be two-and-a-half times as large as normal. Microdissection confirmed the present of larger but fewer nephrons. The "Oligoméganéphronie" of one kidney was accompanied by agenesis of the other, which substantiates the presumption that "Oligoméganéphronie" can be accompanied by anomalies like agenesis of the contralateral kidney. The hypertrophy of the glomeruli in this case is compensatory to the agenesis of one kidney and sparsity of glomeruli in the other. The available literature on clinical and anatomo-pathological observations in such cases, is reviewed.

Since the original description of congenital bilateral renal hypoplasy with compensatory nephronomegaly, called by Royer, Habib and Mathieu (1962) "Oligoméganéphronie", approximately 35 additional cases have been reported in the literature (Callis, Castello, Vidal and de Fortuny, 1970; Fetterman and Habib, 1969; Habib, Courtecuisse, Mathieu and Royer, 1962; Murdaugh and Fetterman, 1971; Roget, Beaudang, Couderc and Lagier, 1965; Royer, Habib, Mathieu and Courtecuisse, 1962; Royer, Habib and Leclerc, 1967; Royer, Habib and Mathieu, 1967; Van Acker, Vincke, Quatacker, Senesael and Van den Brande, 1971). Only two cases (Royer, Habib and Leclerc, 1967; Van Acker, Vincke, Quatacker, Senesael and Van den Brande, 1971) were reported with "Oligoméganéphronie" of one kidney and agenesis of the contralateral kidney. In two cases (Fetterman and Habib, 1969; Murdaugh and Fetterman, 1971) microdissection was performed and reported to confirm the light microscopic impression of few and large nephrons as the basic pathology of this condition.

Each new case contributes to the alertness in diagnosing this condition and to its understanding. An additional case of "Oligoméganéphronie", with agenesis of the other kidney, studied by microdissection, was thought to be worthwile to report.

Case Report

An $8^1/_2$ year old boy was admitted to the Department of Paediatrics for evaluation of complaints of weakness, irritability, anorexia and retardation in height and weight development, since the age of two years.

The parents are unrelated, healthy farmers. Five siblings are healthy. The patient is a product of a normal pregnancy and delivery. His birth weight was 3150 g. He was breast fed for three months. Psychomotor development was normal and his general health was satisfactory. At 4 months of age he started to vomit frequently, but the attending physician's examinations failed to reveal any abnormal clinical or laboratory findings. The tendency for vomiting subsided at the age of two years, but at that time it was noticed that the child became irritable, easily tired, lost appetite, did not gain weight, nor grow normally.

At the age of 5 years urine was examined for the first time and found to contain traces of protein, few leucocytes and erythrocytes. Repeated blood urea estimations showed values of 50 to 80 mg/100 ml. The child was told to abstain from eating meat, fish and eggs.

At the age of $8^1/_2$ years the child was brought to the hospital on his parents' initiative. They observed that the boy was passing large quantities of urine and was always willing to drink water.

On admission, a vivacious, clever, restless boy was seen. His height was 109 cm (3rd percentile for 6 years); weight was 21 kg (50th percentile for 6 years); his nutritional state was satisfactory. No pathology was found on the skin and the lymph glands were not enlarged. Ears were large but normal in shape and position. The eyes were slightly exophthalmic; fundoscopy was normal. The chest was symmetric; lungs and heart normal. Blood pressure on repeated examinations found to be 110/80 mm/Hg. Peripheral pulses were normally palpated. The abdomen was soft and non tender. No masses were palpable. The left kidney was easily palpated, but no kidney could be felt on the right. Liver and spleen were not enlarged. Genitalia, rectal examination, extremities and neurological examination were without pathological alterations.

Laboratory Findings. Urine examination: The daily output was around 1200 cc; urine osmolality was 340 mOsm/kg water (plasma osmolality 285 to 304 mOsm/kg water); urine pH was 5.5; repeated urinalysis revealed traces of protein, few leucocytes and erythrocytes; urine cultures were negative. Amino acid excretion in the urine was normal. Blood urea was 54 to 85 mg/100 ml, uric acid 7.3 mg/100 ml, plasma creatinine 1.2 mg/100 ml, creatinine clearance (corrected for body surface) 50 ml/min; Electrolytes, carbon dioxide, total proteins, albumin/globulin ratio, calcium, phosphorus, alkaline phosphatase were all normal. Fasting blood glucose was normal. The haemoglobin was 13.2 gm/100 ml, white blood count 7200/100 ml with normal differential count. Chest, skull, sella turcica and skeletal X-ray surveys were described as normal. Bone age corresponded to 6 years (chronological age $8^1/_2$).

The flat film of the abdomen showed the presence of a kidney of normal shape and size on the left side. No kidney was seen on the right side. After administration of the contrast material (and subsequently a "drip" IVP), very weak excretion could be seen, by the left kidney only, which was retained in the parenchyma of the kidney.

Cystoscopy revealed a hemi-trigonum on the left side, with a normal left uretero-vesical opening.

A kidney needle biopsy and subsequently an open kidney biopsy were performed, with the parents' consent.

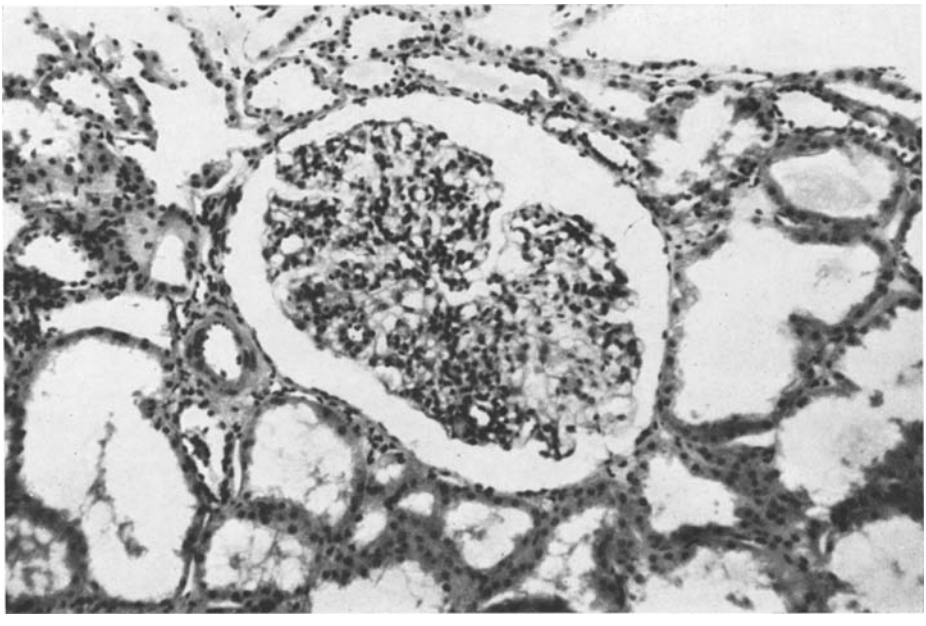

Fig. 1. Large, quite normal looking glomerulus and enlarged tubuli. H. E. ×250

Pathological Investigation

A. Light Microscopy. For this examination, two needle biopsy pieces were received. Both together were of 1 cm length. Only renal cortex was seen in the tissue received.

Despite the quite adequate size of the biopsy a total of only 5 glomeruli were found. The distance between the glomeruli was greater than normal. The most striking finding in them was their size (Fig. 1). The mean diameter of the glomeruli, at the widest point, was 340 μ, with a range of 280 μ to 400 μ. The measurement was taken from one side of the Bowman capsule to the other. The mean diameter of the glomeruli of the normal kidney of a 9 year old child was found, by the same method of measurement, to be 120 μ. The measurements were performed by the method described by Elias and Hennig (1967).

The glomerular Bowman capsules in the patient's kidney were not thickened. The number of cells in the glomerular tuft was increased, but not superimposed or crowded. The capillaries were patent, with thin walls, the mesangial region of the glomeruli slightly accentuated. The juxta-glomerular apparatus could not be assessed as none was found in the slides examined. No hyalinised or obsolescent glomeruli were found. The tubuli were large, with empty lumen. The tubular epithelium looked normal with slight flattening of the cells. In one of the tubuli a hyaline cast was found.

The interstitial tissue was without pathological changes, except two small areas of focal fibrosis and round cell infiltration. No pathological alteration was found in the blood vessels.

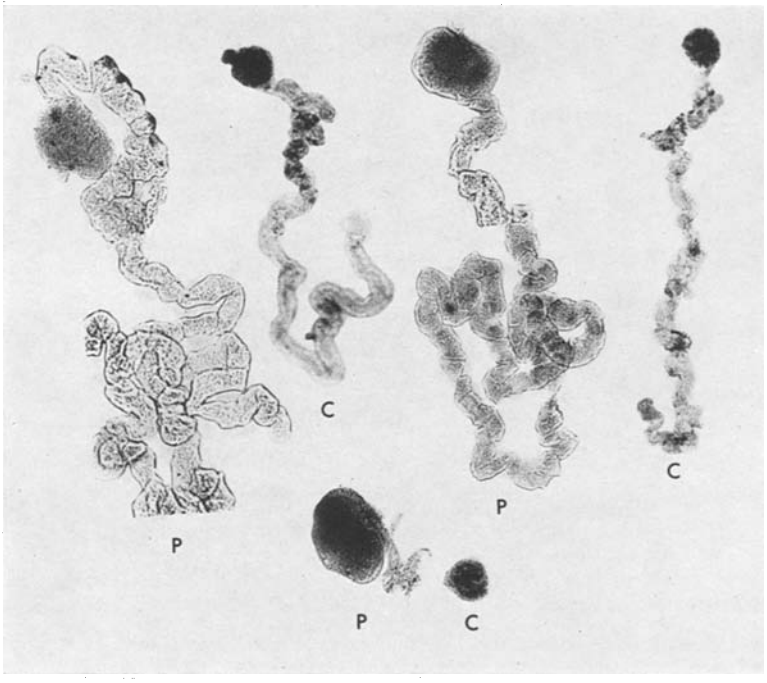

Fig. 2. Microdissected glomeruli and part of the tubuli from the patient's kidney (*P*) and from a normal kidney of the same age (*C*). The patient's glomeruli are outstanding larger than the control's. ×45

B. Microdissection was performed on a $^1/_2 \times ^1/_2 \times ^1/_2$ cm size cubicle of renal cortex removed by open biopsy. The method used for the microdissection was that described by Oliver and Macdowell (1951).

Only 9 glomeruli were found. 5 of them could not be dissected connected to their tubules and were photographed separately. The other 4 glomeruli were dissected attached to part of their tubules. Microdissections of an autopsied normal kidney, from a 9 year old child, were photographed for comparison (Fig. 2).

A striking difference in the diameter of the glomeruli of the patient and the normal kidney could be seen, the patient's glomeruli being much larger. The proximal convoluted tubules of the patient's kidney were more tortuous and wider than the control kidney tubules. It was not possible to compare the size or length of the other parts of the nephron, as they could not be dissected entirely in the patient's kidney. No tubular diverticuli were found in the dissected tubuli of the malformed kidney.

Discussion

Royer and Habib in 1962 defined as oligoméganéphronie a congenital malformation of the kidney consisting of fewer than normal nephrones, with compensatory hypertrophy of their size.

The clinical picture of eight cases of this condition was described in detail and assembled into a table by Royer, Habib and Mathieu (1967) in the book "Nephrologie im Kindesalter", and twenty-one cases were described by Royer, Habib and Leclerc (1967) in the Proceedings of the Third International Congress of Nephrology. The four cases described by Van Acker *et al.* (1971) had similar clinical manifestations. Vomiting in early life, beginning in the first year, with slowly developing renal insufficiency, is characteristic in all cases. This renal insufficiency manifests itself clinically mainly by polyuria and polydipsia. Blood pressure is normal; it was reported temporarily slightly elevated in only one case (case no. 6 of Royer *et al.*, 1967). In later life, with the aggravation of the kidney insufficiency, anaemia may appear. One of the most uniform complaints of the parents of these children is growth retardation (in weight and height).

The characteristic laboratory findings in all cases are the abnormalities in concentrating ability, in acid-base-balance and in some of the cases, in calcium metabolism. The urine contains a moderate quantity of proteins. Haematuria or the finding of casts in the urine, is not frequent or characteristic.

Uremia is an early biochemical finding. It fluctuates, influenced by many pre-renal situations, such as vomiting or infections. The creatinine clearance and creatinine in blood are normal or slightly altered over a period of years; any significant alteration of it is a bad prognostic sign.

A slightly atypical case was reported by Callis *et al.* (1970), in which edema and haematuria were the presenting symptoms.

The condition is a congenital one but is not genetically determined. No kidney or other organ malformations were described in the patients' families, except the finding of unilateral hypoplasia of the kidney in a sibling of one of the case of Van Acker *et al.* (1971) (case no. 4).

The case presented here is clinically quite typical and seems to be in the quite early phase of a progressive renal insufficiency. Royer *et al.* (1967) divided the clinical and parallel histological findings, by the severity of such findings, into three stages.

Approximately half of the cases in the literature are described macroscopically and light microscopically in kidneys from post-mortem examination or nephrectomies. The ages of these children are in the early teens or in the later years of the first decade. The other descriptions are from cases in whom the kidney material was received by biopsies, and the age range of this patients is also from 5 to 16 years. No description of the condition was found in the literature on newborns or in very early life. The reason for this is that despite the presumption that the condition is a congenital one, its functional effects are slowly progressive and lead to chronic renal failure and death in the early teens and not in the first years of life.

In the material from cases of young children the striking pathology is the decrease in the number of glomeruli and increase in their size. Later some hyalinized glomeruli can be found. The tubuli are large, with flat epithelial cells. No pathology is found in the interstitium of the kidneys from young patients; later small areas of fibrosis and cellular infiltrate can be detected, progressing to quite severe interstitial fibrosis in cases dying from renal failure.

Objective measurements of the sparsity and size of the glomeruli are reported by Royer *et al.* (1967) and Fetterman and Habib (1969). The number of the glomeruli is five times less than normal in Royer's cases and the mean diameter of the glomeruli 2.25 times larger than in a normal kidney of a similar age. Elias and Hennig (1967) measured the diameter of the Bowman capsule from routine hematoxylin-eosin sections and found it to be 70 μ in the 6 months infant, 136 μ in the 7 year old and 168 μ in the 47 year old.

Our measurement of the normal glomerulus in one 9 year old child died accidentally, using the method of Elias and Hennig, showed a mean diameter of 120 μ. In the patient's kidney, the same method of measurement, showed an average diameter of 340 μ, so that in our case the size of the glomeruli was more than two and a half times greater than normal. In one case of Fetterman and Habib (1969), glomerulometric studies were performed by Palkovits and Zolnai (1969). They found only one fifth of the normal number of glomeruli in the kidneys of patients with oligoméganéphronie.

No glomerulometric study was performed in our case, since the whole received piece of kidney tissue was microdissected, but the finding of 9 glomeruli in a 0.125 cm^3 piece of renal cortex is very suggestive for oligonéphronie.

Confirmation of the existence of large glomeruli and tubuli by microdissection in cases of "Oligoméganéphronie" was reported by Fetterman and Habib (1969) and Murdaugh and Fetterman (1971). The same authors found that the mean length of the proximal convoluted tubules was four times greater than normal and the mean volume seventeen times greater. They came to the conclusion, by calculating the glomerulotubular balance, that the proximal convoluted tubules had become disproportionately enlarged in relation to the glomeruli and that the "heterogeneity of the nephrons in regard to glomerulo-tubular relationships is no greater than that in a normal kidney."

Our microdissection study confirmed the large diameter of the glomeruli seen in the light microscopy and the presence of a tortuous and large proximal convoluted tubule.

In the above mentioned case of microdissection, Fetterman and Habib (1969) found diverticles in the proximal convoluted tubules. They considered these a manifestation of the hypertrophy and hyperplasy. No diverticles were found in our case, probably because our case is younger than Fetterman's case ($8^1/_2$/13) and diverticles of proximal convoluted tubules appear later in the life of this kind of patients. In Fetterman's case (1971) the possibility of an adjunct malformation in the form of these diverticles cannot be ruled out.

Royer *et al.* (1962, 1967), in all their reports and articles on oligoméganéphronie, referred to it as "bilateral congenital".

In view of the fact that in our case, by intravenous pyelography, clinical palpation and cystoscopy an absence of the right kidney and ureter was found, the diagnosis of oligoméganéphronie was hesitant.

Unilateral agenesis of the kidney is a quite frequent anomaly, as it occurs in 1 in 100 to 1 in 4000 individuals (Heptinstall, 1966). It is frequently accompanied by malformations of other organs and causes no functional impairment. The contralateral kidney in these cases is hypertrophic or normal in size with normal number of nephrons. Chronic renal insufficiency appears in unilateral

agenetic cases only when the contralateral kidney is infected, traumatized or other pathological processes attacks the single hypertrophic kidney. No progressive renal insufficiency, as in our case, was described in unilateral kidney agenesis.

Considering all the clinical, laboratory and morphological findings we feel ourselves justified to diagnose the case as a unilateral "Oligoméganéphronie" with agenesis of the contralateral kidney.

Our case is the third with oligoméganéphronie of one kidney and concomitant agenesis of the other. The first case was reported in Royer *et al*'s series (1967) and the second by Van Acker *et al.* (1971). The appearance of cases with other congenital malformations, such as in case no. 4 of Van Acker's series, substantiates the presumption that "Oligoméganéphronie" is a congenital anomaly which may be solitary or accompanied by congenital anomalies of other organs or the other kidney. It is interesting to note that no cases of congenital malformation of the contralateral kidney, other than agenesis, have been published. The anomaly in oligoméganéphronie is most probably, as presumed by Van Acker *et al.*, a limitation in number of the embryonic formation of the nephrons and the hypertrophy is compensatory. In our case the glomerular hypertrophy must be considered compensatory to the agenesis of the right kidney and the oligonéphronie of the other kidney. It will be interesting to find "segmental uni or bilateral oligoméganéphronie" if such condition exists at all.

The pathological changes in the glomeruli in the later stages of the disease can be explained by stress glomerulitis (Hauptmann, 1965), or what the German literature calls "Überlastungsglomerulitis" (Zollinger, 1966), and may be attributed to "overtaxation" of the glomerulus.

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